SURGERY OF THE ADRENAL GLANDS

Publication Number 227

AMERICAN LECTURE SERIES®

A Monograph in

AMERICAN LECTURES IN ABDOMINAL VISCERA

Edited by

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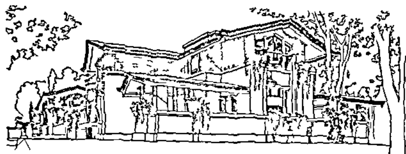
SURGERY OF THE ADRENAL GLANDS

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Figures 1 and 2 From Arey L B *Developmental Anatomy* Philadelphia Saunders 1950

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Figures 12A 12B and 12C From Steinbach H L Lyon R P Smith D R and Miller E R Extraperitoneal pneumography *Radiology* 59 167 1952

Figures 13 16A 16B 21A and 21B From Wilkins L *The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence* Springfield Charles C Thomas Publisher 1950

Figures 16A 21A and 21B From Wilkins L A feminizing adrenal tumor causing gynecomastia in a boy of five years contrasted with a virilizing tumor in a five year old girl *J Clin Endocrinol* *8* 111 132 1948

Figures 19A and 19B From Howard J E and Whitehill M R Virilism—a case report and discussion *Internat Clin* *4* 51 1937

Figure 20 Courtesy of Dr Mark M Ravitch

Figures 23 and 36 From Huggins and Bergenstal Surgery of the adrenals *J A M A* *147* 101 106 1951

Figure 26 Courtesy of Dr Willard E Goodwin and Dr Elmer Belt

Figure 29A Courtesy of Dr Glenn Morrow

Figure 35 From Wilkins L and Ravitch M Adrenocortical tumor arising in the liver of a three year old boy with signs of virilism and Cushing s syndrome *Pediatrics* 9 671 1952

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SURGERY OF THE ADRENAL GLANDS

I

INTRODUCTION

During the last 30 years remarkable advances have been made in our knowledge of the normal and abnormal adrenal gland These have included among many recognition and successful surgical treatment of functioning tumors of both the adrenal cortex and medulla isolation and synthesis of a number of crystalline adrenal hormones utilization of these steroids in the treatment of adrenal insufficiency secondary to disease or removal of the adrenals extensive exploration of the biologic properties of these compounds in health and disease and inquiry into the effects of partial and complete adrenalectomy in several disease states Whereas it is beyond the scope of this monograph to review adequately the mass of clinical and laboratory data which pertain to these advances it is necessary to present in an abbreviated fashion certain current concepts of adrenal function which relate to the diagnosis and treatment of adrenal states amenable to surgical therapy

In presenting the clinical picture of patients with adrenal tumors representative examples have been chosen and their clinical histories given in detail This is done in the belief that this method of presentation provides a clearer picture of each condition than that which is furnished by a listing of the frequency of symptoms in a large

II

DEVELOPMENT

ACCORDING TO Witschi[149] in birds and reptiles where the origin of the adrenal is most easily studied the adrenal cortex arises from dorsally situated strings of cells derived from the blastema cords along the median borders of the mesonephric bodies Ventrally situated cells from the same area take part in the formation of the primordial gonad folds contributing the medulla of the gonad Thus the adrenal cortex and gonad medulla have a common origin in the mesonephric blastema and are of *mesodermal* origin This common origin of adrenal cortex and gonad medulla the latter giving rise to the interstitial cells of the testis or the theca cells of the ovary has caused several authors to suggest that at times cells potentially capable of forming gonadal hormones may be included in the adrenal

In man the first traces of the adrenal cortex are found at the beginning of the fourth week of life (6 mm embryo) at which time cells which lie between the mesonephric fold and the root of the mesentery begin to proliferate[110 134] At this time and for a short time thereafter coelomic epithelium is in direct continuity with subjacent mesenchyme (Figure 1 A and B) Rapid growth occurs and at 12 mm prominent mesenchymal condensations are evident (Figure 1 C Figure 2 A and B) With fur

series of cases It will become evident that many of the examples presented have been studied by our colleagues particularly Dr Lawson Wilkins and Dr John Eager Howard We are indebted to them not only for permission to use case material but also for their unfailing cooperation in the clinical management of these and other patients with adrenal disorders We are convinced that this cooperation between internist and surgeon cannot be emphasized too strongly We are also deeply indebted to the many scholars in medicine who have done so much to increase the accuracy of diagnosis of adrenal disorders and to improve treatment We have given credit where credit seemed due

We hope that the reader will profit directly from this presentation and more important that he will be stimulated to read authoritative source material presently available and appearing in increasing volume

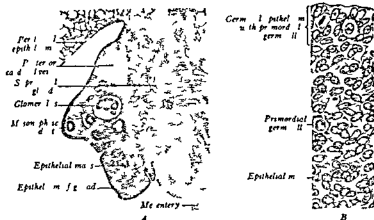


Figure 2 Indifferent stage of the human gonad illustrated by transverse sections A at 12 mm including associated regions (after Prentiss x82) B at 12 mm showing structural details (x550)

brings them to the center of the gland and at birth arrangement in cords is complete In the elasmobranch fish the cortex and medulla exist as separate glands un joined in amphibians reptiles and birds the chromaffin cells are scattered through the mesodermal tissue only in mammals is a definite medulla encapsulated by cortex

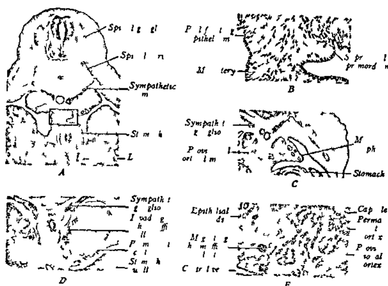
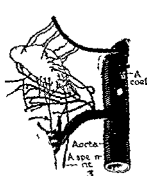
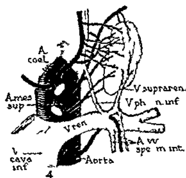


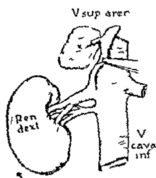
Figure 1 Development of the human suprarenal gland shown in transverse sections A at 8 mm (x24) B detail of area marked by a rectangle in A (x75) C at 12 mm (x20) D at 16 mm (x24) E at four months (x70)

ther increase in size the enlarging adrenal cortex projects from the dorsal wall of the coelom between the urogenital organs and the mesentery Here they continue to enlarge becoming relatively huge In an eight weeks embryo the adrenal is as large as the kidney and at birth is one third as large

The adrenal medulla is of *ectodermal* origin arising in common with sympathetic ganglion cells from primitive cell masses of the neural crest In human embryos of 16 mm when the provisional cortical mass is surrounded by permanent cortex masses of cells derived from the primitive sympathetic ganglia grow ventrally and penetrate the cortical primordium on its medial side (Figure 1 A B C D and E) At this stage they begin to exhibit the chromaffin reaction Continued migration of these cells







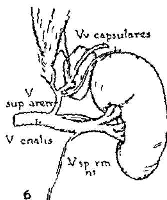


Figure 3 Renal and suprarenal arteries right side
Figure 4 Renal suprarenal and associated arteries and veins left side

Figure 5 Renal and suprarenal veins right side Suprarenal vein as regularly is short renal vein pictured represents a relatively uncommon arrangement

Figure 6 Renal suprarenal and tributary veins left side Renal vein of standard type receives suprarenal phrenic and capsular drainage cranially caudally it receives gonadal (here spermatic) vein

cortex can be divided histologically from without inward into three vaguely defined layers the zona glomerulosa zona fasciculata and zona reticularis (Figure 7) Based on the distribution of doubly refracting lipid drop

III

STRUCTURE

IN THE ADULT the adrenal glands are paired yellowish in color, flattened and triangular to semilunar in shape measure approximately 4 0 x 2 5 x 0 5 centimeters weigh 3 5 to 5 0 grams each and are situated at the cranial end of each kidney Atrophy can be recognized grossly the gland appearing paler thinner and smaller than the normal but hyperplasia may be difficult to recognize either grossly or microscopically

The blood supply is considerable and variable Anson *et al*[6] have shown that the adrenal arteries derived from the inferior phrenic aortic and renal arteries may be exceedingly numerous at times their number attaining a total of 50 or more at the periphery of the gland (Figures 3 and 4) No similarity in pattern exists between arteries and veins Whereas adrenal arteries are numerous and small adrenal veins are single large and constant in pattern On the right side the adrenal vein is short and empties directly into the vena cava (Figure 5) On the left side the vein is longer commonly joins the inferior phrenic and empties into the renal vein opposite the termination of the internal spermatic (Figure 6) Grollman[30] and others[39,43] have described the circulation within the gland itself Owing to differences in arrangement and shapes of the constituent cells the adrenal

tivity However according to Sayers[119] The battery of specialized staining technics which have been applied to the adrenal has contributed little more to our knowledge of the chemistry and physiology of the adrenal cortex than has the simple Sudan method It is recognized that the amount of lipid present as measured by intensity of Sudan stain may not parallel material exhibiting steroid reactions (birefringence fluorescence Schiff reaction[7 11 47]) However until more is known about the chemical nature of the latter materials it is wise to withhold physio logical interpretations Statements regarding storage and secretion of ketosteroids have contributed nothing but confusion to the field Furthermore he considers it pre mature to assign distinct secretory functions to the zones when the problem of the nature of the secretion of the adrenal cortex is not yet settled"

Newer technics should aid in this regard particularly if applied to fresh adrenal tissue rather than that oxidized by fixation Some believe that the mitochondria are in volved in hormone production

The border between the cortex and medulla is made irregular by projections of columns of cortical cells into the medulla The irregularly shaped cells of the medulla are arranged in closely packed groups surrounded by si nusoidal venules As early as 1856 Vulpian[139] noted a striking difference in the staining reaction of the cells of the cortex and medulla the latter turning green when immersed in a solution of ferric chloride Shortly there after Henle[5] noted that when adrenal tissue was allowed to react with dilute solutions of potassium dichromate certain granules in the medullary cells appeared brown ish red with precipitate This is the so called chromaf fin reaction" and is explained on the basis of reduction of dichromate to insoluble chromium dioxide by epine phrine or a precursor It appears to some that the chro

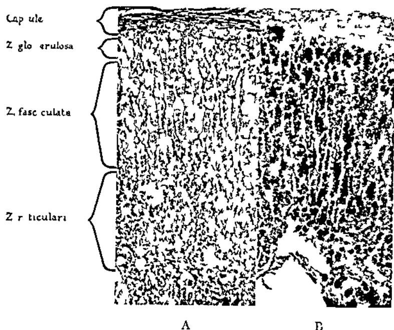


Figure 7 Sections of the adrenal gland of a normal adult male A hematoxylin and eosin (x75) B oil red O and eosin (x75)

lets in certain cells of the cortex Weaver and Nelson[14] have defined four zones The epithelial cells comprising these layers vary from groups of small columnar cells in the glomerulosa to larger polyhedral cells arranged in columns in the fasciculata to large dark and small light cells in the reticularis According to Hoerr[1] these dark and light cells are especially evident in the guinea pig There seems to be fair unanimity of opinion that the cells of the cortex originate in the zona glomerulosa and as they develop migrate inward to degenerate in the most inward layer the zona reticularis

Numerous histologic technics have been devised in an effort to identify and localize the steroids of the adrenal cortex and to measure their functional and secretory ac

IV

FUNCTION

THE ADRENAL CORTEX

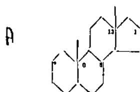
FOR A DETAILED discussion of the physiology of the adrenal cortex the reader is referred to the extensive writings of Albright[3] Ingle[1] Kendall[74] Long[88] Sayers[119] Selye[1] and others However a few observations relating to adrenal cortical function will be outlined including those functions which seem to be altered in the chronic hyperfunctioning state commonly observed in the patient with adrenal hyperplasia or tumor Admittedly in cases of hyperplasia or tumor we may be dealing with an aberrant secretory activity which has no necessary relation to the normal physiology of the adrenal cortex

All workers agree that the adrenal cortex unlike the medulla is essential for life and that such essentiality depends on the elaboration of a hormonal substance or substances by the gland To date although 28 crystalline steroids have been isolated from adrenal tissue it is not clear which steroid or combination of steroids is normally elaborated by the cortex or which is necessary for life Some investigators believe that one parent hormone is elaborated and in turn its metabolites exert observed functions of known crystalline steroids others believe that several different steroids are made and individually secreted into the blood stream Of importance is the observation

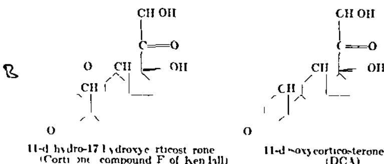
maffin reaction is roughly proportional to the epinephrine content of the gland. Of interest to the subsequent discussion of medullary tumors of the adrenal is Karsner's[73] view that a diagnosis of a pheochromocytoma is not valid without a positive chromaffin reaction.

a carbonyl or an hydroxyl group There are four known examples of this the most studied being 11 dehydro 17 hydroxycorticosterone known also as cortisone or compound E of Kendall (Figure 8)B

Steroids having androgen estrogen and progestational actions have been isolated from the adrenal gland Examples are androsterone estrone and progesterone Normally estrogen and progestational actions appear to be relatively weak and quantitatively these steroids make up only a small percentage of the total steroidal material of the adrenal However it will be seen that in certain pathologic states notably hyperplasia and tumor feminizing changes occur and urinary estrogens may be increased Adrenal androgens appear to be concerned with the growth of axillary and pubic hair and with muscular vigor



Common basic ring system



11-dehydro-17 hydroxycorticosterone (Cortisone compound E of Kendall)

11-desoxycorticosterone (DCA)

Figure 8 Basic steroid ring system illustrating the component rings and the conventional number assigned to the individual carbon atoms Below are two crystalline adrenal cortical steroids

that the amorphous fraction which remains after all crystalline steroids have been separated from cortical extracts is still capable of sustaining life in the adrenalectomized animal With the increasing availability of crystalline adrenal steroids it may well be that important discoveries will be made concerning which hormone is most effective in maintaining life The recent work of Thorn *et al*[13] and Huggins and Bergenstal[64] attests to this Both groups have succeeded in maintaining life in humans after bilateral adrenalectomy with compound E (cortisone) a feat which was extremely difficult when only cortical extracts and desoxycorticosterone acetate were available (Huggins and Scott)[69]

Present knowledge indicates that the adrenal cortex is concerned in part with a number of metabolic activities which include 1) the metabolism of sodium potassium chloride and water 2) certain aspects of the metabolism of carbohydrate protein and fat and 3) activities similar to those produced by certain gonadal hormones Activities described under headings 1) and 2) have been labeled corticoid and those under heading 3) as androgenic estrogenic and progestational

All crystalline adrenal cortical steroids have a common basic structure as shown in Figure 8A which in turn is common to certain gonadal hormones cholesterol and vitamin D Differences in action appear to depend in part upon modification of this nucleus primarily in position 3 11 and 17 Thus the chief example of a steroid having a pronounced effect on mineral metabolism is 11 desoxycorticosterone (Figure 8C) This compound has little effect on carbohydrate metabolism and structurally is seen to lack an oxygen atom at position 11

Steroids which in part are concerned with catabolism of protein and gluconeogenesis have in common an oxygen atom at position 11 this oxygen being in the form of

malize plasma sodium regardless of the direction of the deviation from normal whereas DCA acts unidirectionally to produce sodium retention

More will be said concerning possible androgen production by the adrenal later on when the rationale for bilateral adrenalectomy in the treatment of disseminated prostatic cancer is discussed At this point a brief discussion of urinary 17 ketosteroids and corticoids seems warranted to aid in a discussion of the physiology of the normal adrenal cortex and in the diagnosis of the clinical conditions of adrenal cortical hyperplasia and tumor

Urinary 17 Ketosteroids

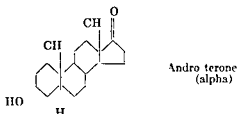
Urinary steroids of the general configuration of those already shown in Figure 8 but having a ketone group in position 17 are known as 17 ketosteroids Such steroids when allowed to act with *meta* dinitrobenzene in alkaline solution (Zimmermann reaction) give rise to a magenta color which can be measured quantitatively The method of extraction separation and determination which we now rely upon is essentially as follows

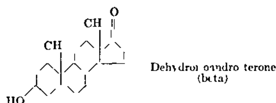
The urine is collected in glass bottles containing 10 ml of concentrated hydrochloric acid as a preservative Subsequently a 100 ml aliquot is hydrolyzed by boiling for 20 minutes after addition of 0 1 of its volume of concentrated hydrochloric acid It is then cooled quickly and extracted by shaking with ether in a centrifuge bottle Shaking is accomplished by a mechanical shaker and separation by centrifugation and aspiration of the supernatant ether layer This ether layer is then washed several times with base in order to remove acids and phenols This extract after acidification washing with water evaporating to dryness and solution in absolute alcohol is termed the neutral extract" and is ready for colorimetric determination of the total neutral 17 ketosteroids To 0 2 ml of test

Furthermore they are believed to be responsible for the total amount of urinary 17 ketosteroids found in the urine of women and roughly two thirds of that found in the urine of men *(vide infra)*

At this point it appears appropriate to pause and to introduce a direct quotation from a recent review article by Ingle[71] entitled *The Biological Properties of Cortisone* This should serve to emphasize that rigid assignment of function to crystalline adrenal cortical steroids should be avoided whether these steroids are elaborated by the normal cortex or the cortex involved in hyperplasia or tumor Ingle states If any one fact has been made evident about cortisone it is that this substance affects many different tissues and physiologic processes of the body At a time when the physiology of the adrenal cortex seemed more simple cortisone and related 11 oxygenated steroids were tagged as S or sugar hormones or glucocorticoids The author is not without sin in this matter of describing an elephant in terms of shape of its tail and was among the students of endocrinology who found these characterizations useful but he believes that this is an appropriate time to abandon the concept that cortisone is concerned principally with carbohydrate metabolism and to explore each of its many biologic properties in search for new concepts of its action As an antidote for an era of oversimplification in adrenal physiology the author recommends the masterful review of the adrenal cortex and homeostasis by Sayers [119]

In this review Sayers[119] cites many investigations in support of new concepts of cortisone action Thus Lossham *et al*[41] have shown that cortisone will maintain serum electrolytes within the normal range in most patients whose adrenals have been removed whereas desoxycorticosterone (DCA) usually will not This fits in with the concept of Woodbury *et al*[1] that cortisone can nor





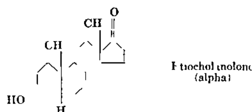


Figure 9 Structural formulae of three normally occurring neutral urinary 17 ketosteroids They are characterized as *alpha* or *beta* 17 ketosteroids depending on the *alpha* ( ) or *beta* (——) orientation of the OH group at the third carbon

Normal men excrete on an average more 17 keto steroids than do normal women Whereas daily variations are appreciable our average values are 14 mg per 24 hours for men and 9 mg for women This difference an average of 5 mg is believed to represent the amount derived from the testes the 9 mg is thought to originate in the adrenal cortex of both sexes Evidence indicates that the amount contributed by the ovaries is very small Women with severe adrenal insufficiency excrete very little of these compounds Thus it would appear that the

solution in an Evelyn colorimeter tube is added 0 2 ml of a 2 per cent solution of *meta* dinitrobenzene and 0 2 ml of 2 5 N potassium hydroxide both in absolute alcohol The color is developed in the dark at 25 C for 80 minutes and after dilution with 10 ml of absolute alcohol the intensity of color is determined in the Evelyn colorimeter using a 520 mμ filter Absolute alcohol is substituted for the neutral extract in the blank Dehydroisoandrosterone is used to prepare standards and as a reference

Little difficulty has been encountered with the method except in preserving the alcoholic potassium hydroxide solution However we have found as have Wilson and Carter [148] that this solution will keep well if ascorbic acid *is added and if stored under nitrogen*

Whereas a number of these steroids exist in the urine of normal individuals three predominate androsterone its isomer etiocholanolone and dehydroisoandrosterone (Figure 9) Androsterone and etiocholanolone appear in about equal quantities and in greater concentration than dehydroisoandrosterone Androsterone is a stronger androgen on bioassay than dehydroisoandrosterone (approximately three times) Etiocholanolone is inactive Because of this and other examples which could be given it is important to emphasize that *all urinary 17 ketosteroids are not androgens*

Due to spatial variations of the hydroxyl group in position 3 17 ketosteroids are divisible into *alpha* and *beta* fractions *Beta* 17 ketosteroids are precipitated with digitonin and can be measured colorimetrically [5, 31, 4] Androsterone and etiocholanolone are *alpha* 17 ketosteroids dehydroisoandrosterone is a *beta* 17 ketosteroid Whereas normally 0 to 15 per cent of the total level of 17 ketosteroids consists of the *beta* fraction in certain altered states to be described this fraction constitutes a much greater percentage of the total

Those having similar biological properties on bioassay have been named biocorticoids; those having similar chemical properties by chemical assay have been designated chemocorticoids.

Urinary Biocorticoids. Suitable extracts of human urine when injected into the adrenalectomized animal will effect several actions characteristic of certain adrenal cortical extracts and crystalline steroids. Thus they may maintain life,[137] prevent water intoxication,[1 0] promote deposition of glycogen in the liver,[33] prolong survival from exposure to cold,[34] and improve work performance.[1 4] Quantitative bioassays based on cold protection and liver glycogen deposition have been developed and are referred to as the CP test and the LGD test, respectively. Whereas the LGD test is less sensitive than the CP test, it is more accurate.[34, 13] Apparently both measure essentially the same thing, for corticosteroids possessing an oxygen atom at position 11 will promote glycogen deposition and prolong survival from exposure to cold.

Although there is a close correlation between the rate of urinary excretion of these biocorticoids and the activity of the adrenal cortex as judged clinically, these procedures require precise technic and are time consuming. Consequently they are not practical in most clinical laboratories.

Urinary Chemocorticoids. The chemical technics used to estimate urinary chemocorticoids are based on the ability of a number of steroids to reduce copper or phosphomolybdic acid,[4] or to generate formaldehyde by reaction with periodic acid.[3, 89] Based on these properties urinary lipids have been given the designation CRL if they reduce copper, PRL if they reduce phosphomolybdic acid, and FL if they generate formaldehyde.

For example, steroids containing a primary or secondary *alpha* ketol group, an *alpha*, *beta* unsaturated 3

testes and the adrenals are the principal sources of the urinary 17 ketosteroids Direct evidence for this (admittedly complicated by severe malignant disease) is found in the single adult male studied by Huggins and Scott[63] This individual survived bilateral adrenalectomy after previous castration for approximately four months without cortisone therapy and total urinary 17 ketosteroids fell to extremely low levels

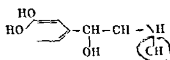
Whereas it seems reasonably clear that the testes and the adrenal cortex are responsible for these steroids their precursors in these organs are poorly understood Some clinicians have considered the urinary 17 ketosteroids to be an index of androgenic activity of these structures but it must be again emphasized that all urinary 17 ketosteroids are not biological androgens Furthermore recent evidence suggests that cortisone itself is degraded by the liver and other tissues to 17 ketosteroids and perhaps even androgens Thus the administration of ACTH or cortisone leads to a rise in these urinary elements

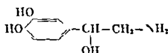
Whereas it will be clear that the determination of total urinary 17 ketosteroids and the *beta* fraction are of considerable importance as laboratory aids in the diagnosis of certain disorders of the testes and adrenals it would appear at present that their output is not a sensitive measure of changing rates of secretion of cortical hormone by the adrenal cortex in man particularly over short periods of time Recent evidence suggests that the measurement of urinary corticoids may prove superior and that as a consequence a brief discussion of these substances seems justified

Urinary Corticoids

The term urinary corticoid has been used to describe substances in urine which are not clearly identified but which possess certain properties of the cortical hormones

Extracts of the adrenal medulla capable of causing a pronounced rise in blood pressure upon injection were first prepared by Oliver and Schäfer [103] in 1895. In 1901 Takamine [131] and Aldrich [4] independently succeeded in isolating crystalline l-adrenaline to which Aldrich assigned the correct empiric formula $C_9H_{13}O_3N$. Due to the efforts of many including the synthesis of racemic adrenaline by Stoltz [1 8] and Dakin [0] in 1905 the structural formula shown below was established





EPINEPHRINE (Adrenaline)

NOREPINEPHRINE (Arterenol)

The term "epinephrine" proposed by Abel [1] remains "official" for the natural substance. 1902

Whereas it is beyond the scope of this monograph to discuss at length the various metabolic changes secondary to the administration of epinephrine – such as increases in blood sugar, blood lactic acid and basal metabolic rate – a brief description of its "sympathomimetic" action should aid in the subsequent discussion of the diagnosis and treatment of functioning adrenal medullary tumors.

An understanding of sympathomimetic action presupposes a familiarity with current concepts of neurohumoral transmission in the autonomic nervous system. On *anatomic* grounds the autonomic nervous system may be divided into parasympathetic (craniosacral) and sympathetic (thoracolumbar) divisions. On *functional* grounds division is made on the basis of the nature of the substance liberated in the region of the postganglionic nerve ending of all autonomic nerve fibers, whether excitatory or inhibitory. At present many believe that acetylcholine

ketone group or both will reduce phosphomolybdic acid. In this category are to be found a number of biologically active steroids including cortisone, desoxycortisone and progesterone, as well as a large number of biologically inactive steroids. Copper is reduced by steroids containing an *alpha* ketol group but an *alpha beta* unsaturated 3 ketone group does not react.[4] Formaldehyde is liberated from 20 21 *alpha* ketols and glycols by oxidation with periodic acid.[35, 89]

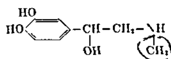
Until recently the above methods have been applied to chloroform or chloroform ether extracts of urine and measure the chemocorticoid present in the free state. Since 1951 several laboratories[6, 113, 136] have investigated procedures designed to measure conjugated (and total) urinary corticosteroids in addition to the free moiety. Those interested should read the article by Reddy, Jenkins and Thorn.[113] They believe that their method measures only total 17 hydroxycorticoids. If so, many nonspecific substances will be eliminated and a better correlation should be possible between chemocorticoid excretion and the clinical estimate of adrenal cortical activity as well as with the level of urinary biocorticoids.

One distinct advantage of the chemical methods over those involving bioassay is their simplicity, making them suitable for routine determination in the clinical laboratory. The next few years should see a greater application of these studies in known states of adrenal function and should permit a more accurate evaluation of their worth.

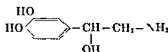
THE ADRENAL MEDULLA

Most of our knowledge of medullary function is based on laboratory and clinical observations following the injection of epinephrine or on the measurement of epinephrine and epinephrine like substances in the blood during various physiologic manipulations.

Extracts of the adrenal medulla capable of causing a pronounced rise in blood pressure upon injection were first prepared by Oliver and Schafer[103] in 1895. In 1901 Takamine[131] and Aldrich[4] independently succeeded in isolating crystalline l-adrenaline to which Aldrich assigned the correct empiric formula $C_9H_{13}O_3N$. Due to the efforts of many, including the synthesis of racemic adrenaline by Stoltz[128] and Dakin[30] in 1905, the structural formula shown below was established.



EPINEPHRINE
(Adrenaline)



NOREPINEPHRINE
(Arterenol)

The term "epinephrine," proposed by Abel[1] 1902 remains official for the natural substance.

Whereas it is beyond the scope of this monograph to discuss at length the various metabolic changes secondary to the administration of epinephrine — such as increases in blood sugar, blood lactic acid and basal metabolic rate — a brief description of its sympathomimetic action should aid in the subsequent discussion of the diagnosis and treatment of functioning adrenal medullary tumors.

An understanding of sympathomimetic action presupposes a familiarity with current concepts of neurohumoral transmission in the autonomic nervous system. On *anatomic* grounds the autonomic nervous system may be divided into parasympathetic (craniosacral) and sympathetic (thoracolumbar) divisions. On *functional* grounds division is made on the basis of the nature of the substance liberated in the region of the postganglionic nerve ending of all autonomic nerve fibers, whether excitatory or inhibitory. At present many believe that acetylcholine

is liberated at all postganglionic parasympathetic nerve endings resulting in transmission between the nerve fiber and receptor in the cell (myoneural junction) Such fibers have been termed cholinergic

Whereas the majority of postganglionic sympathetic nerve fibers liberate an adrenaline like substance and are known as adrenergic types some sympathetic fibers — such as those innervating vasodilator fibers and the sweat glands in some species — are cholinergic (Figure 10) Sympathomimetic implies mimicry of only those actions of the adrenergic type whether excitatory or inhibitory but not cholinergic sympathetic action Some of the more important sympathomimetic actions of epinephrine are cardiac acceleration arteriolar constriction pupillary dilation salivary secretion relaxation of bronchial musculature and inhibition of the urinary detrusor

According to the late W B Cannon and his school excitatory or inhibitory actions of the adrenergic type depend upon the combination of epinephrine with either

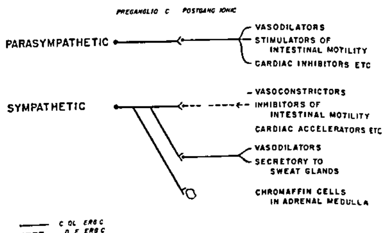
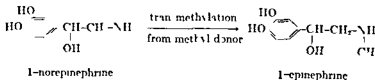


Figure 10 Schematic representation of the autonomic nerve fibers indicating the sites of action presumed nature of the chemical mediator and types of response

an excitatory substance E or an inhibitory substance I at the receptor with the formation of sympathin E and "sympathin I respectively Recently a number of reports have appeared which tend to clarify this mechanism

After Abel's[1] characterization of epinephrine most conceded that it represented the pressor component of the adrenal medulla and some believed epinephrine and sympathin I were identical although the pharmacologic action of epinephrine was not strictly that observed following sympathetic nerve stimulation Subsequent to this Barger and Dale[10] synthesized a large number of *beta* phenylethylamine analogs which on test showed a general similarity of action to that observed following sympathetic nerve stimulation and to which they gave the designation sympathomimetic amines Among these were epinephrine and norepinephrine the latter differing in structure from epinephrine by absence of a methyl group attached to nitrogen at the end of the side chain (Nitrogen Ohne Radical) as shown above Although Barger and Dale pointed out biologic differences in these two compounds it remained for Bacq[9] to suggest that the action of norepinephrine simulated the properties of sympathin E

It now appears to most workers that on stimulation some sympathetic nerve fibers release only epinephrine others liberate only norepinephrine and still other adrenergic nerve endings yield both Furthermore it seems likely that most adrenergic nerves are capable of transmethylating norepinephrine thus forming epinephrine



l-norepinephrine l-epinephrine

These observations and speculations are particularly interesting in view of the finding of Goldenberg *et al*[44] and others [13, 59] that epinephrine extracts from normal adrenal glands as well as from pheochromocytomas may contain relatively large amounts of norepinephrine at times as much as 50 to 90 per cent This may result from an impairment of norepinephrine transmethylation

In passing it is of interest to note that pharmacologically dibenamine one of the drugs used to test patients for the presence of a pheochromocytoma acts only against norepinephrine not epinephrine Hence it would be reasonable to assume that if a pheochromocytoma were producing mainly epinephrine such a competitor as dibenamine might give a false negative test

V

TUMORS OF THE ADRENAL GLAND

VARIOUS CLASSIFICATIONS have been proposed for tumors arising within the adrenal cortex and medulla Generally such have been based on either the microscopic appearance of the tumor or the signs and symptoms observed in patients with proved tumors

ANATOMIC CLASSIFICATION

The anatomic classifications of Karsner [73] and Stout [1 9] appear to be the most recent and complete and the reader is referred to their original manuscripts for details In brief all tumors are separated into two broad divisions 1) heterologous and 2) homologous and the latter subdivided into cortical and medullary

Heterologous Tumors

Heterologous tumors are those derived from tissues within the gland which are not peculiar to the adrenal and which may occur in any other gland These include fibroma lipoma neuroma neurofibroma myoma hemangioma lymphangioma myelolipoma and melanoma Karsner believes that osteomas probably represent metaplasia following inflammation or hemorrhage and that the spindle and giant cell sarcomas reported in the earlier literature probably were anaplastic carcinomas and sympathicogoniomas respectively

Homologous Tumors

Cortical Tumors The principal tumors arising from the adrenal cortex are the cortical nodule the cortical adenoma and the cortical carcinoma The so called cortical nodule or hamartoma resembles closely the cortical adenoma but is usually smaller multiple bilateral and somewhat more regular in cellular arrangement Both are benign and are usually encapsulated The origin of the adenoma is obscure some believing that it arises from primitive cortical cells and others from mature cortical cells It may possibly arise from a cortical nodule

Cortical carcinomas are distinguished from cortical adenomas primarily on histological evidence of invasion and clinical evidence of metastasis

Examples of the histology of cortical adenomas and carcinomas as well as certain medullary tumors will be presented below under representative clinical cases

Medullary Tumors Under this heading most authors group all tumors which seem to arise from the sympathogonia a primitive cell common to sympathetic ganglia and the adrenal medulla or to one of its descendants According to Bielshowsky [14] the sympathogonia may differentiate along two lines forming the sympathoblast and the pheochromoblast Each in turn may give rise to the sympathetic ganglion cell and pheochromocyte respectively the latter being known as a chromaffin cell and positively identified only by the chromaffin reaction Tumors arise from all these cells and the preponderant cell type forms the stem for the descriptive term used thus sympathicogonioma sympathicoblastoma ganglioneuroma and pheochromocytoma

Some authors group sympathicogoniomas and sympathicoblastomas together under the heading neuroblastoma and Stout classes neuroblastomas and differentiated

and undifferentiated sympathicogoniomas under sympathicoblastoma

Ganglioneuromas have been described as differentiated ganglioneuroma (benign) and partially differentiated ganglioneuroma (malignant) by Stout and ganglioneuroma (generally benign) and malignant ganglioneuroma by Karsner

The term paraganglioma is used by many synonymously *with pheochromocytoma Stout prefers to* call hormonally active tumors of the paraganglionic group pheochromocytomas and all inactive ones paragangliomas in each instance naming the region or tissue of origin an example of the latter being a paraganglioma of the carotid body

If a pheochromocytoma shows histologic invasiveness or clinical metastasis some use the term pheochromoblastoma

FUNCTIONAL CLASSIFICATION

Several authors including Cahill *et al*[6] Kenyon[7] and Wilkins[146] have divided adrenal cortical tumors into two main groups according to whether or not they are hormonally active (with subdivision of the latter group according to the symptom complexes observed) Medullary tumors can also be divided into two main groups on the basis of their hormonal activity but subdivision of the functional group is not yet possible For pedagogic reasons such a classification offers certain advantages but it should not be too rigid As Kepler and Locke[78] have so aptly expressed it such a classification may "have the disadvantage of developing unconscious psychologic barriers which confine thinking to artificially *imposed limitations* With reservations and without originality the following classification is presented

Cortical Tumors

1. Tumors with no recognizable hormonal activity
2. Tumors having hormonal activity leading to
   - A. Cushing's syndrome with or without virilization
   - B. Virilization
     - i. In the male child
     - ii. In the female child
     - iii. In the adult female
   - C. Feminization
     - i. In the male child
     - ii. In the adult male

Medullary Tumors

1. Tumors with no recognizable hormonal activity
2. Tumors having hormonal activity

Hormonally Inactive Cortical Tumors

We have had little personal experience with tumors in this group and have not reviewed the literature in this regard. According to Cahill,[9] Hartung, Macera, Stevenson, Gibson and others have reported tumors of the adrenal cortex which have occurred without recognizable hormonal changes. In his most recent review with Melicow,[1] Cahill cites his personal experience in a total of six. All were without symptoms except for pain which was secondary to the large size of the tumor or to metastases. They were found as the result of routine examination, abdominal exploration or autopsy. Perirenal air insufflation aided in the diagnosis of two. On pathologic examination four were carcinomas, one a sarcoma and one an adenoma. Only the latter survived treatment which consisted of transperitoneal excision of the tumor.

Figure 11 is a photomicrograph of a peculiar tumor

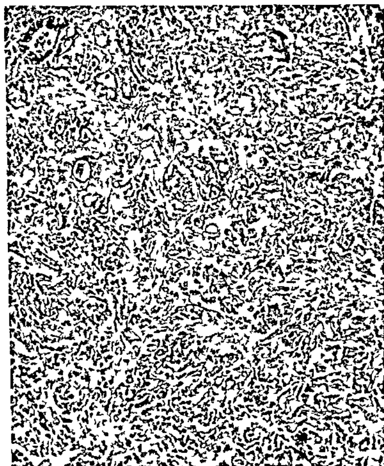


Figure 11 Photomicrograph (x200) of a hormonally inactive cortical tumor found at autopsy

of the right adrenal an incidental finding at autopsy in a 64 year old male who died on the twelfth postoperative day of a massive pulmonary embolus following a simple perineal enucleation of a benign nodular hyperplastic prostate gland (S A R History No 76187 The Johns Hopkins Hospital) Grossly this tumor measured 3 cm

in diameter projected from the surface of the adrenal on section was white and rubbery and possessed a delicate fibrous capsule The adrenal cortex although thinned out over the tumor was histologically normal A careful re view of the history failed to reveal any signs or symptoms suggesting that this tumor was hormonally active

Hormonally Active Cortical Tumors

In certain stages of development nearly all cases of excessive function (hyperadrenocorticism) may be di vided into two main groups on the basis of their pre dominant signs and symptoms These two groups are 1) the *adrenogenital syndrome* and 2) *Cushings syn drome*

Wilkins [14] defines the adrenogenital syndrome as a disorder in which there are evidences of excessive pro duction of adrenal androgen with either (a) no evidence of disturbed cortin production or (b) a deficiency of cortins (corticoids), and Cushings syndrome as a dis order in which signs of excessive cortin production pre dominate with usually some evidence of androgen and occasionally increased estrin

In view of the multiplicity of hormones which the adrenal cortex may produce it is not surprising that a great variety of signs and symptoms may be observed or that there may be gradations between types By and large the symptom complex observed depends upon the nature of the substance elaborated the time in develop ment at which this excess function begins and the sex of the patient

Cushings Syndrome Cushings syndrome is a term now used by most authors to describe a symptom com plex without regard for etiology The clinical manifesta tions of this syndrome are identical with those originally described by Cushing [9] found in association with baso

philic adenomas of the pituitary (Cushing's disease or pituitary basophilism) Although the syndrome occurs in young women with greatest frequency men and children of either sex are not immune Prominent features of the disease are buffalo obesity a term used to describe a characteristic body habitus in which muscular wasting and redistribution of fat leads to apparent obesity of the head and neck and trunk particularly the abdomen while sparing the extremities excessive growth of hair without other evidence of masculinization vascular hypertension diabetes osteoporosis and suppression of sexual function in the form of amenorrhea or impotence Colorful similes such as moon face pig eye and sun fish mouth have been suggested to describe the facial expressions Purplish striae may be present over the abdomen The skin may be atrophic and mottled Acne may be present Kyphosis may result from demineralization of the thoracic spine Polyuria may be a prominent feature

Examination of the blood may reveal no abnormality However lymphopenia is nearly always present and erythremia may be Serum sodium may rise and potassium may fall Occasionally hypochloremic alkalosis is present with or without change in serum sodium

The total neutral urinary 17 ketosteroids are often normal but may show moderate to marked increase depending somewhat on the basic cause of the syndrome These together with values for the so called *beta* fraction will be discussed later Urinary biocorticoids and chemocorticoids are often increased

The pathogenesis of Cushing's syndrome is most intriguing and the interested reader is referred to the account of the late Edwin J Kepler [78] who wrote in such a delightful fashion On theoretical grounds Kepler regarded all cases of Cushing's syndrome as a manifesta

tion of adrenal cortical hyperfunction regardless of anatomic findings and even in the presence of a basophilic pituitary tumor (Cushing's disease) believing that if the adrenal cortices were absent the patient would have few if any symptoms of the syndrome in spite of the fact that his disease continued to be present On anatomic grounds Kepler presents the probable gross and microscopic findings in a given series of patients with Cushing's syndrome or disease as follows In almost 100 per cent of cases Crooke's changes will be found in the baso philic cells of the pituitary in only 10 per cent of cases will these be the only findings in the pituitary or adrenal In approximately 50 per cent of cases a basophilic adenoma of the pituitary will be found This is usually small and may require serial section to find it may be large and erode the sella turcica Of those with pituitary tumors one third may have demonstrable hyperplasia of the adrenal cortex In one in three of the entire series one may find a benign or a malignant adrenal tumor or merely enlarged and presumably hyperplastic adrenal cortices In some three per cent enlarged adrenals and a thymic tumor may be found and rarely an aberrant adrenal tumor or ovarian tumor

The Diagnosis of Cushing's Syndrome

Signs and Symptoms The appearance of a patient with advanced Cushing's disease is usually so characteristic as to make the diagnosis rather simple Given an individual with this appearance and in whom several of the prominent features described such as hypertension diabetes osteoporosis etc are found the diagnosis is established The cause remains to be determined At the outset we wish to emphasize that we know of no sure way to determine whether an adrenal tumor or adrenal cortical hyperplasia is responsible for the syndrome

short of surgical exploration However several clinical rules of thumb as well as certain laboratory procedures though not infallible aid in making a preoperative diagnosis

Generally patients with all the characteristic features of Cushing's syndrome have adrenal hyperplasia those with mixed clinical pictures particularly those with moderate to severe virilization usually have an adrenal tumor An enlarged clitoris in an uncomplicated Cushing's syndrome usually speaks for tumor Female pseudohermaphrodites almost always have congenital adrenal cortical hyperplasia and not tumor Greatest difficulty arises in determining the cause of simple hirsutism particularly if associated with obesity hypertension and menstrual irregularities Such patients demand a careful diagnostic study

Laboratory Aids Special laboratory studies in addition to the determination of serum sodium potassium chlorides calcium phosphorus carbon dioxide combining power non protein nitrogen and glucose include x rays of the skull long bones and thoracolumbar spine intravenous (and at times retrograde) pyelograms perirenal insufflation of air aortograms laminograms and the determination of urinary 17 ketosteroids (including *alpha* and *beta* fractions) 11 oxysteroids (corticoids) and urinary estroids or estrogens

Provided an adrenal tumor is large pyelograms may show downward displacement of the kidney In the hands of those experienced with the method (Cahill[19] Roome[114] Mencher[91] and Vest[138]) perirenal air insufflation films have been useful and without complications or fatalities

Recently several clinicians have advocated perirenal and extraperitoneal pneumography via the paracoccygeal route [17] There follows a brief description of the technic used by Steinbach *et al* [17]

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With the patient in the side position legs drawn up the anus is anesthetized with anesthetic ointment the injection site prepared with antiseptic solution and procaine injected in the midline between anus and coccyx 1 2 cm from the latter A No 18 or 19 spinal needle is inserted through skin and subcutaneous tissue until the tip impinges on the tip of the coccyx The index finger of the free hand is placed in the rectum and the needle is redirected to slide along the anterior surface of the coccyx and through the anococcygeal raphe (Figures 12A and B) The needle is inserted another 2 3 cm care being taken to avoid injury to the rectum A few cubic centimeters of air is inserted to check the position The injection set consisting of a bottle of oxygen and a bottle of water is attached to the needle through a sterile section of rubber tubing (Figure 12C) The oxygen is allowed to flow in at a pressure of 15 20 cm water The volume of oxygen needed varies with the patient About 15 cc /kg body weight of oxygen is enough to visualize both sides of the body If an extraperitoneal pneumogram of a single side of the body is required that side is kept in the superior position since the oxygen rises to the highest portion of the extraperitoneal tissue If a generalized pneumogram is desired half the gas is injected with one side elevated and half with the other side elevated

"X rays can be taken as soon as the injection is completed optimal time is two hours after injection

In our experience several tumors have been visualized on laminograms and aortograms *(Vide infra)*

Estimation of the levels of certain urinary steroids is of distinct value in the differential diagnosis of adrenal hyperplasia and tumor In this regard the interested reader is referred to the writings of Mason and Engstrom[91] Munson *et al*[95] Forbes and Albright[40] Gardner and Migeon[4] and Landau[84] A few salient points follow

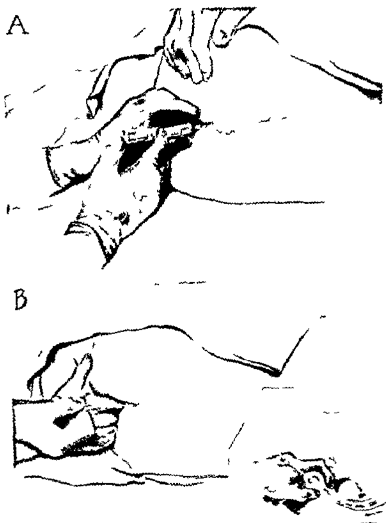


Figure 12 A and B The spinal needle is first inserted until the tip impinges upon the tip of the coccyx The index finger of the opposite hand is placed in the rectum and the needle is redirected so as to slide along the anterior surface of the coccyx and through the anococcygeal raphe

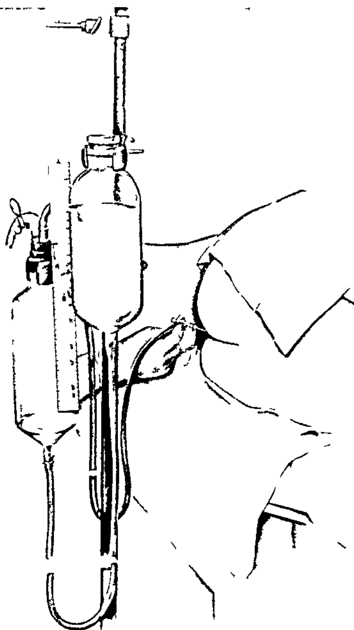


Figure 12 C (*See legend on opposite page.*)

Adrenal cortical tumors are often associated with an increase in urinary 17 ketosteroids Mason and Engstrom[91] found only two exceptions to this in a review of 50 cases in the literature and in these two poor preservation of the urine and extreme illness respectively may well have been responsible Not included in this survey were two others recently studied by Mason who also had normal values In one evidence of increased cortical function was found in an increased excretion of corticosteroids

Forbes and Albright[40] in a recent review of 90 cases of Cushing s syndrome in whom the adrenals were visualized and classified according to pathologic change found the average 17 ketosteroid excretion to be without tumor 18 1 with benign tumor 5 7 and with malignant tumor 124 4 mg per 24 hours"

Whereas total urinary 17 ketosteroids may be elevated in adrenal hyperplasia as a rule they are not as high as in cases of adrenal tumor Furthermore although no 17 ketosteroid has been found which is characteristic of either condition the *beta* fraction is more frequently elevated in cases of tumor and dehydroisoandrosterone is more readily isolated * In this regard Mason and Engstrom[91] sum up the available data as follows Thus data now available suggests that a daily excretion of more than 50 mg of 17 ketosteroids 50 per cent or more of which is *beta* fraction indicates the presence of an adrenal cortical tumor Fine distinctions and sharp lines of demarcation cannot be made

Pregnanetriol (pregnane 3 (*alpha*) 17 20 triol) has been isolated from the urine of seven cases of adrenal hyperplasia and in one case in which a clinical diagnosis of adrenal cortical tumor was made Unfortunately in the latter instance the diagnosis of tumor was not confirmed by laparotomy or autopsy[90]

←

Figure 12 C The injection set up is attached to the needle through a sterile section of rubber tubing and a cotton filter Oxygen is allowed to flow in at a pressure of 15 to 20 cm of water

Recent studies by Gardner and Migeon[4] working in Wilkins laboratory have a distinct bearing on the problem Using a color test for dehydroisoandrosterone like compounds initially suggested by Dirscherl and Zilliken[31] and developed by Allen *et al* they were able to confirm the latters findings of positive tests in adrenal cortical tumor patients but not in adrenal hyperplasia although total 17 ketosteroids were high in both groups and the results of *beta* separation with digitonin were equivocal Furthermore when cortisone was given urinary 17 ketosteroids were reduced to normal values in children with hyperplasia (two cases) but not in cases of adrenal cortical tumor in children (two cases)

Lastly Wilkins[146] has found the determination of neutral reducing lipids of the urine (formerly called 11 oxysteroids) to be of some diagnostic importance He lists the following values children – 0 3 to 0 6 mg per 24 hours adults – 0 5 to 1 0 andrenogenital syndrome – 0 5 to 2 0 and Cushings syndrome – 2 0 to 5 0

Cushings Syndrome in Children

In his masterful treatise on endocrine disorders in childhood Wilkins[146] reviews the reported cases of Cushings syndrome in children listing 26 under the age of 10 years All in this group had tumors[1] After the age of 10 the syndrome was found in association with adrenal tumor adrenal hyperplasia or a basophilic adenoma of the pituitary By and large the symptom complex in children is similar to that seen in the adult To illustrate the salient features the following case is presented in detail

---

[1] As always nothing is 100 per cent In an article whi[illegible] after Wilkins book Albright and associates[illegible] state The [illegible] tient with Cushings syndrome due to adrenal hyperplasia [illegible] authors have been able to find was an eight year-old girl H[illegible] they do maintain that Adrenal tumor is the only cause of C[illegible] syndrome recorded in infants and small children"

This female infant in addition to Cushing s syndrome showed moderately severe masculinization as evidenced by marked hirsutism and moderate enlargement of the clitoris

G F History No A 55822 Harriet Lane Home for Invalid Children of The Johns Hopkins Hospital born January 28 1947 was seen in the pediatric endocrine clinic The Johns Hopkins Hospital by Dr Lawson Wilkins on July 12 1947 at the age of 5½ months At three months of age the parents noted that her cheeks were fat and that she was developing acne of her face and scalp Several weeks later hair was noted on the upper lip followed in several weeks by the appearance of hair in the region of the genitals A gradual enlargement of the abdomen was observed over the course of several months and vocal utterances were observed to be somewhat deep Dr Wilkins description of body build and proportions skin hair and sexual development are classic and are as follows

This baby is of average size for her age and has normal skeletal proportions She presents a very striking appearance because of her marked obesity Although she is only 3 lbs above the average weight she presents a characteristic buffalo type of obesity There is a huge fat face with bulging cheeks between which there is a tiny stubby nose Cheeks and chin are so fat as to almost hide her neck There is immense padding of fat over her shoulder upper back and chest The abdomen is distended and somewhat obese The legs although fat are much less so than the upper trunk and face (Figure 13)

Her face is very red There is marked acneform eruption consisting of pustules and papules over the forehead cheeks and extending up into the scalp Skin in this region seems very oily and her scalp and hair are oily There is no acne lesion on the body

"She has abundant black hair on the scalp which grows down low on her forehead almost to her eyebrows Eye

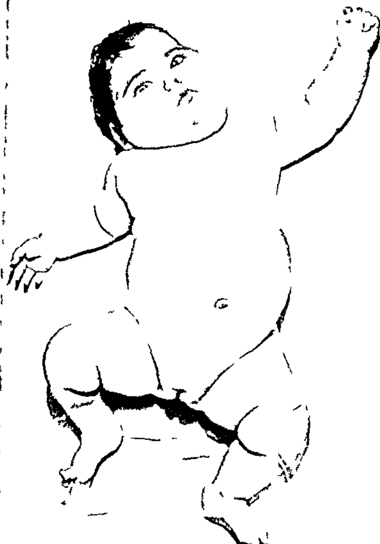


Figure 13. Cushings syndrome associated with an adr[illegible] carcinoma in a female age five months. Normal genit[illegible]. Characteristic facies of two months duration. Blood pr[illegible] 180/110 to 210/120. Total 17 ketosteroids 77 mg. per day. Mildly diabetic glucose tolerance curve. Large mass in region of right →

brows are thick and black almost meeting in the mid line There is fine black down on her upper lip some on the upper chin and fine sideburns extend down on her cheeks There is a heavy growth of long fine black hair over her back especially in the upper region There is some coarse black hair on the labia and a little fine black hair in the axilla

Her cry is rather deep and hoarse The areolae measure about 1 cm in diameter and are somewhat brownish The nipples are undeveloped and no mammary tissue is palpable The labia majora are greatly hypertrophied and show marked pigmentation There is a moderate growth of coarse dark hair 2 to 3 cm in length on the labia The clitoris is considerably enlarged measures 2 cm in length is much thicker than the average with plainly visible glans and hypertrophied preputial folds and shows a tendency to erections The labia minora are entirely infantile and undeveloped There is distinctly separate urethral and vaginal orifice of normal infantile configuration"

General examination revealed a palpable mass in the right upper quadrant and flank which was felt to represent a normal kidney displaced downward medially and anteriorly by a retroperitoneal mass The blood pressure on several examinations ranged from 180/120 to 210/110

Laboratory data revealed the following abnormal findings A moderate polycythemia a moderate leucocytosis a mild diabetic glucose tolerance curve and 77 mg total neutral urinary 17 ketosteroids per 24 hours An intravenous pyelogram was unsatisfactory However retrograde pyelograms revealed a normal left kidney and a normal right kidney displaced downward and anteriorly by a large right upper quadrant mass The initial chest

nal on pyelogram Child died six months after operation Blood sure and 17 ketosteroids falling after operation returned to ormally high levels prior to death (Courtesy of Dr Lawson Wilkins The Johns Hopkins Hospital)

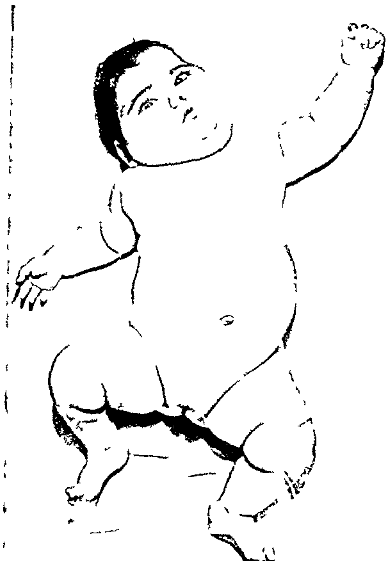


Figure 13. Cushing's syndrome associated with an adrenal cortical carcinoma in a female age five months. Normal genitalia at birth. Characteristic facies of two months duration. Blood pressure 180/110 to 210/120. Total 17 ketosteroids 77 mg per day. Mildly diabetic glucose tolerance curve. Large mass in region of right →

Prior to operation the infant received 3000 roentgen units measured in air (5 x 200 anteriorly and 10 x 300 posteriorly over the tumor area) without apparent effect on the size of the tumor. Of considerable interest was the observation that on the day prior to x-ray therapy she excreted 55.1 mg. total neutral urinary 17-ketosteroids per 24 hours and immediately after cessation of the 15 treatments described 105.3 mg. per day.

On July 24, 1947, excision of an adrenal tumor was carried out through a right upper abdominal transverse incision extending from the left of the midline laterally into the right flank. No metastases could be found in the abdomen. Special pre- and postoperative therapy, so important in all adrenal surgery, was carried out and the patient made an uneventful recovery. In that this varied but little from an established routine to be described subsequently, it is not presented separately.

Grossly the tumor was well encapsulated and weighed 250 grams. Histologically (Figure 14) the tumor resembled closely adrenal cortex and a renal carcinoma (hypernephroma), being made up of clear cells with dark staining nuclei. An abundance of lipid within these cells was evident on fat stain. Histologically it was not possible to tell whether or not the tumor was malignant and the final pathologic diagnosis was adrenal cortical tumor.

Following section 250 grams of tumor were extracted with carbon tetrachloride and after appropriate separation a Zimmerman reaction run (Dr. Roger Lewis). This revealed 56 mg. of 17-ketosteroid in the entire tumor. Ten days postoperatively urinary 17-ketosteroids had risen to 62.4 mg. per 24 hours. On November 25, 1947, four months after operation, the infant expired. Autopsy was refused.

The Treatment of Cushing's Syndrome

Surgical. Since it is not possible to determine with certainty the cause of Cushing's syndrome, an explora

x-ray was read as normal and x-rays of the long bones showed approximately normal osseous development.

A diagnosis of an "adrenal tumor manifesting evidence of excessive secretion of both corticoids and androgen was made. Normal configuration of the urethra and vagina excluded the possibility of congenital adrenal hyperplasia and female pseudohermaphroditism.



Figure 14. Photomicrograph (x75) of an adrenal cortical carcinoma causing Cushing's syndrome in the female infant shown in Figure 13.

taken by mouth Four grams of salt daily should be added to the diet Shortly all special therapy can be discontinued As in cases of operative removal of pheochromocytomas (which see) postoperative hypotension can be combatted with a continuous infusion of dilute epinephrine norepinephrine or neosynephrine

Subtotal Adrenalectomy In those cases of Cushing s syndrome in which a tumor is not found generally in the past treatment has been unsatisfactory If caused by a basophilic adenoma of the pituitary or adrenal cortical hyperplasia other methods have been used These have included pituitary irradiation in an effort to inhibit the production of ACTH androgen administration for its protein anabolic action as well as its reparative effect on bone matrix estrogen administration (usually with androgen) to increase calcification and subtotal and total adrenalectomy in an effort to overcome hyperfunction of the adrenal cortex Improvement has been reported after these various forms of treatment but it is difficult to assess because of spontaneous variations in the course of the disease For a splendid discussion of the natural history of Cushing s syndrome the reader is referred to a recent article with this title by Plotz *et al*[103] Until recently little data were available to aid in assessing the value of subtotal adrenalectomy

Our own experience does not permit us to discuss subtotal adrenalectomy for Cushing s syndrome intelligently but we wish to refer to a comprehensive article on the subject by Priestley *et al*[111] as well as a previous communication by E J Kepler[6] The summary of the article by Priestley and his associates is quoted *in extenso* "Extensive bilateral subtotal adrenalectomy has been performed in 29 cases of Cushing s syndrome in which surgical exploration failed to reveal a functioning adrenal cortical tumor There were six postoperative deaths all

tion of both adrenals should always be performed If a cortical adenoma or localized cortical carcinoma is found surgical excision offers a good chance for cure Preferred surgical routes for various types of adrenal cortical and medullary tumors will be presented subsequently

According to most observers functioning cortical tumors resulting in Cushing's syndrome are almost always associated with some degree of atrophy of the contralateral adrenal Consequently strict attention must be given to proper supportive therapy Since the advent of cortisone management has been much less of a problem Whereas it is impossible to set forth a rigid system of management certain suggestions may be made regarding the administration of adrenal hormones electrolytes glucose and fluid

In adults with Cushing's syndrome in whom a unilateral tumor has been demonstrated preoperatively or in those in whom it is felt that a tumor is most likely present we recommend the following substitution therapy

> The night before the operation the patient is given 50 mg cortisone acetate 3 mg desoxycorticosterone acetate (DCA) and 5 grams of salt Just prior to surgery 100 mg cortisone acetate and 5 mg DCA are given parenterally During operation 1000 cc of 5 per cent glucose is given intravenously and whole blood if necessary This is followed by 500 cc of 5 per cent glucose in normal saline For the first 24 hours additional fluid in the form of 5 per cent glucose is injected to make a total of 3000 cc Cortisone acetate 50 mg every four to six hours completes substitution therapy for the day of operation During the succeeding 24 hours 3000 cc of 5 per cent glucose is given intravenously one sixth of which is in normal saline cortisone acetate 50 mg every six hours is continued and one dose of 3 mg DCA is given Usually within 72 hours after operation the amount of cortisone can be reduced appreciably DCA stopped altogether and fluids can be

satisfactory remission regrowth may lead to relapse re section of too much tissue leads to adrenal insufficiency requiring replacement therapy which in itself must be balanced nicely Indeed the situation is somewhat anal ogous to surgical therapy for hyperthyroidism and based on this analogy one might predict that results following subtotal adrenalectomy will improve And too as more is learned of the original cause of adrenal hyperfunction greater efforts will be made to find suitable analogs which may obviate surgical maneuvers

Recently several clinicians have suggested total ad renalectomy for Cushing s syndrome

Resume of Surgical Treatment In an attempt to clar ify the approach to the surgical management of Cushing s syndrome Sprague *et al*[1 6] and Albright and his associ ates[91] quite independently have drawn up a formula to follow By and large we agree

1 If the first adrenal gland explored is atrophic al most surely the contralateral gland is involved in tumor

2 If the first adrenal gland explored is large the patient has adrenal hyperplasia and the contralateral gland will be large also

3 If the first adrenal gland explored is normal in size this adrenal and its opposite are probably hyper functioning though not hyperplastic and a contralateral tumor is unlikely

In situation 1 as outlined previously removal of the tumor constitutes therapy In so doing the need for re placement therapy is paramount in situations 2 and 3 subtotal adrenalectomy appears to be the procedure of choice at present of those with the most experience

Virilizing Tumors Adrenal cortical hyperplasia and adrenal cortical tumors may cause virilization rapid

of which occurred prior to the use of cortisone in both the preoperative and postoperative management. Of the 23 remaining patients, one patient experienced no improvement following operation, three patients will require further observation as the postoperative period has been too short to allow evaluation of the results, and 19 patients have obtained an excellent remission of the Cushing's syndrome. However, three of the 19 patients have adrenal insufficiency. In general the results have been encouraging and appear to support the concept that regardless of what the primary etiology of the syndrome may ultimately prove to be, its features are contingent upon hyperfunction of the adrenal cortices. It appears entirely possible that results may be improved in the future.*

Certainly this work emphasizes the importance of the adrenal cortex in the pathogenesis of Cushing's syndrome, as well as the advantage of cortisone over adrenal cortical extracts in the postoperative management of these patients. It also points up the nicety of balance which apparently must be achieved in order to provide a continuous remission. Resection of insufficient adrenal cortex results in failure; resection of sufficient tissue leads to

* After completion of this monograph an article by Sprague, Kvale and Priestley[88] appeared in which they add 21 cases, bringing their total to 50. In their last 27 consecutive cases there has been only one postoperative death, and much of their success they attribute to judicious use of cortisone and desoxycorticosterone acetate. Of a total of 41 patients now living, 40 are judged to be in a state of satisfactory remission. Of these, 20 require replacement therapy in the form of cortisone given orally, and 10 of these 20 require in addition desoxycorticosterone acetate given buccally. Length of remission has ranged from three months to seven years. Several have had a second remission after relapse upon resection of more adrenal tissue. This has prompted the authors to state: "Since it must be presumed that the original [illegible] of adrenal cortical hyperfunction continues to act after a [illegible] has been induced by removal of adrenal tissue, additional recurrences [illegible] be anticipated with the passage of more time."

satisfactory remission regrowth may lead to relapse resection of too much tissue leads to adrenal insufficiency requiring replacement therapy which in itself must be balanced nicely Indeed the situation is somewhat analogous to surgical therapy for hyperthyroidism and based on this analogy one might predict that results following subtotal adrenalectomy will improve And too as more is learned of the original cause of adrenal hyperfunction greater efforts will be made to find suitable analogs which may obviate surgical maneuvers

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growth increased muscularity and accelerated epiphyseal ossification (androgenic effects) and yet be unassociated with signs suggesting hypersecretion of corticoids as seen in Cushing s syndrome Such a syndrome has been called adrenal virilism interrenalism and the adrenogenital syndrome the latter preferred by most

As indicated heretofore the clinical picture observed depends upon the time in development at which excess androgen production occurs and the sex of the patient If adrenal hyperplasia occurs before intrauterine differentiation of the sex organs the resulting abnormality will be either macrogenitosomia precox (congenital adrenal hyperplasia) in the male or pseudohermaphroditism in the female If either adrenal hyperplasia or cortical tumor develops after differentiation of the sex organs the result may be virilization in the female both in the child and the adult and precocious sexual development in the male child

In the Female Child

Incidence To 1948 Wilkins[145] found reports in the literature of 70 cases of adrenal cortical tumors in children Of these 53 were girls 31 with signs and symptoms of uncomplicated adrenogenital syndrome and 22 with findings suggesting Cushing s syndrome He concluded that From the time of birth until the tenth or twelfth year virilization is usually if not always due to adrenal tumor After this age virilization may be due to either tumor or hyperplasia

Diagnosis In contrast to a female pseudohermaphrodite with congenital adrenal hyperplasia at birth a female child with a virilizing tumor has no malformation of the genitourinary apparatus Unlike the female pseudohermaphrodite who shows a urogenital sinus (Figure 15) the female infant with tumor has a normally situated

urethral orifice which is separate and distinct from the vagina and normal infantile female genitalia Virilization secondary to tumor has been observed as early as the third month of life Once in progress development may be quite rapid



Figure 15 Simultaneous demonstration of urogenital sinus vagina urethra and urinary bladder by x ray following the injection of a radio-opaque liquid

We have chosen to illustrate the progress of events in these cases by presenting a representative case

J C History No A 33040 Harriet Lane Home for Invalid Children of The Johns Hopkins Hospital a female age 5½ years was admitted in 1943 to the Endocrine Serv

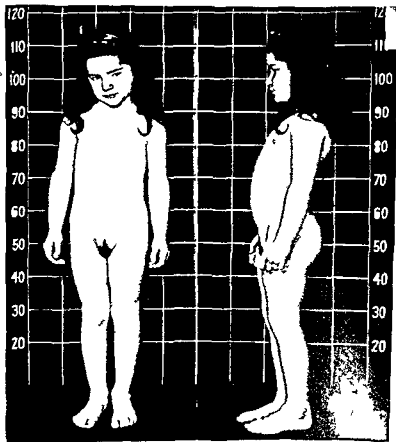


Figure 16 A Virilization in a young girl secondary to an adrenal cortical carcinoma A appearance of the patient five months *after onset* of symptoms and before operation B one year later Reoperation disclosed recurrent tumor (Courtesy of Dr Lawson Wilkins The Johns Hopkins Hospital *J Clin Endocrinol* 8 111 1948)

ice of Dr Lawson Wilkins Six months before the mother had noticed that the clitoris was a little prominent and since had become progressively larger Shortly thereafter pubic hair appeared and continued to grow The voice became deep Although she gained weight rather rapidly

Height 125 cm
normal height for 6½ yrs girl is 117 cm

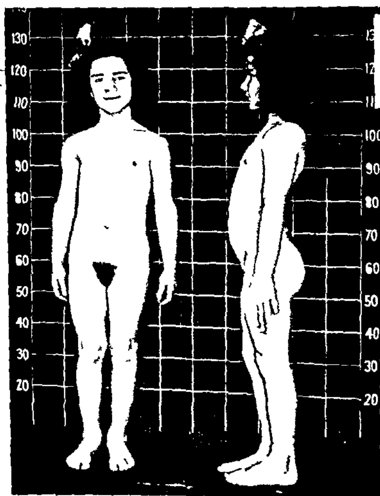


Figure 16 B (*See legend on opposite page.*)

Died 2½ yrs after onset of disease & 2 yr after removal of tumor

she did not become obese The skin became oily and a slight eruption appeared On examination some acne of the face was seen but no unusual amount of facial hair Muscular development seemed advanced Breasts and nipples were infantile and there was no axillary hair Pubic hair was abundant (Figure 16A) and the labia majora and clitoris were markedly enlarged Urethral and vaginal orifices were normally situated On pelvic examination under anesthesia both ovaries and uterus were slightly smaller than for the average child of five years X rays revealed a bone age of seven years a normal sella turcica and normally situated kidneys Values for total 17 ketosteroids ranged from 19 to 22 mg per day the beta fraction constituting less than 1 per cent of the total At operation through a transverse upper abdominal incision a golf ball sized tumor was found springing from the right adrenal This was removed The left adrenal appeared normal Figure 17 shows the microscopic appearance of the tumor which at operation appeared well encapsulated and was described as an adrenal cortical adenoma Except for 10 mg of DCA given prior to operation no hormonal therapy was used Her postoperative convalescence was uneventful and she was discharged from the hospital Within four months the 17 ketosteroids had fallen to 2 1 mg per day However there was no regression of pubic hair (Figure 16B) and the clitoris remained large Within one year after operation the 17 ketosteroids had increased to 94 mg per day and reoperation revealed multiple recurrences of the tumor in the mesentery Within another year the patient expired approximately two years after removal of the original tumor The last 17 ketosteroid determination prior to death showed an excretion of 124 mg per day

Several points are worthy of comment In the differential diagnosis congenital adrenal hyperplasia was excluded on the bases of absence of a urogenital sinus and other defects characteristic of female pseudohermaphro

ditism premature pubarche was excluded by the observations that virilization was progressive the clitoris was enlarged and 17 ketosteroids were abnormally high Recurrence of tumor was predicted by the return of high levels of excretion of total urinary 17 ketosteroids Cortical carcinomas are frequently distinguished from cortical adenomas primarily on histologic evidence of invasion (absent here) and clinical evidence of metastasis (present *one year before death*)

Treatment Provided there is no clinical evidence of metastases surgical excision provides the only cures Often these tumors are malignant metastasizing to the lungs liver and skeleton In cases where the diagnosis is in question early exploration is indicated



Figure 17 Photomicrograph (x200) of adrenal cortical carcinoma causing virilization of young girl shown in Figures 16 A and B

In the Male Child

Incidence In Wilkins study of 70 tumors in children described in part above 17 were boys Of these 12 presented a clinical picture consistent with the diagnosis of adrenogenital syndrome Two showed obesity of the Cushing's type One was feminized and will be described below under the heading Feminizing Tumors

Since this review several additional cases have been reported and others observed including one unreported case seen by us which will be used herein as an illustration of a representative case

Diagnosis One suspects an adrenal cortical tumor in a male child if sexual precocity occurs However early virilization may be secondary to congenital adrenal hyperplasia or an interstitial cell tumor of the testis

Whereas it may be impossible short of surgical exploration to differentiate tumor from congenital hyperplasia several features of the latter may help A familial history of either male or female hyperplasia strongly suggests hyperplasia as does any evidence of adrenal insufficiency such as Addisonian pigmentation Total 17 ketosteroids and particularly the *beta* fraction are usually lower

An interstitial cell tumor of the testis may at times be palpable In questionable cases testicular biopsy is indicated

Again we have chosen to illustrate the main features in the diagnosis by example

H B History No A 84056 Harriet Lane Home for Invalid Children of The Johns Hopkins Hospital a boy aged four years and nine months was admitted in 1951 to the Endocrine Service of Dr Lawson Wilkins and subsequently seen in consultation by one of us Two years before the child's parents had noted enlargement of the

penis and the appearance of pubic hair Shortly there after he was studied at Duke University Hospital where it was recorded that the penis was markedly enlarged sparse pubic hair was present height age was 4 3/4 years x rays of the bones showed accelerated ossification pyelo grams showed the presence of a mass in the left upper quadrant which depressed the left kidney a test for urinary gonadotropins was negative and total urinary 17 ketosteroids ranged from 73 to 144 mg per day 50 to 60 per cent representing the *beta* fraction A diagnosis of adrenal cortical tumor" was made but operation was re fused He returned home and during the two succeeding years the parents noted progressive enlargement of the penis the increase in pubic hair and deepening of the voice He had become very muscular and stronger than his brother who was two years his senior On initial ex amination here his height age was eight years and his bone age 12 years There was marked development of male secondary sexual characteristics (Figure 18 A) with pubic and axillary hair deep voice advanced adolescent de velopment of penis scrotum and prostate but no apparent adolescent development of the testes the size of which were within normal limits for his age The blood pressure varied between 104/54 and 112/72 Urinary 17 ketoster oids ranged from 106 to 194 mg per day and the color test for dehydroisoandrosterone was strongly positive An intravenous pyelogram (Figure 18 B) showed down ward displacement and rotation of the left kidney ap parently due to a mass above it Percutaneous aorto grams were not diagnostic Blood chemistries including serum electrolytes and glucose tolerance were normal A transthoracic operation removed an encapsulated 7 cm adrenal tumor (Figure 18 C) which on section (Figure 18 D) was judged to have arisen from the cortex The postoperative course was uneventful and no hormonal therapy was required The patient has remained well to date and continues to show regression of precocious sexual characteristics

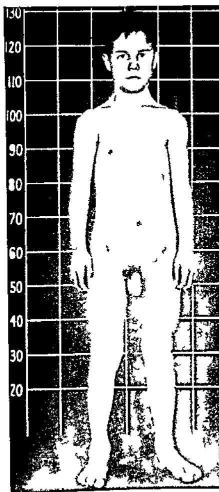


Figure 18 A Virilization associated with an adrenal cortical tumor

has remained well 3 yrs after removal of Tumor

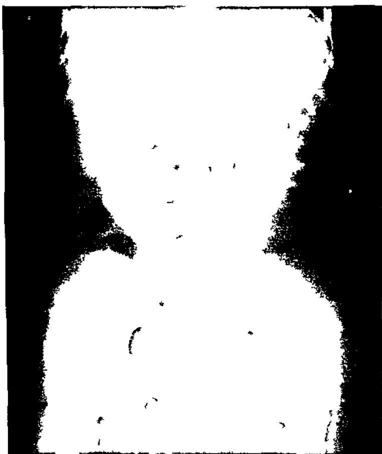


Figure 18 B Intravenous pyelogram showing downward displacement and rotation of the left kidney by the tumor

Here the preoperative diagnosis of a virilizing adrenal cortical tumor was almost certain Masculinization was plainly evident there was no history of congenital adrenal hyperplasia in siblings adrenal insufficiency was not apparent and blood chemistries were normal the kidney was displaced by a probable tumor mass and both total and *beta* 17 ketosteroids were markedly increased The

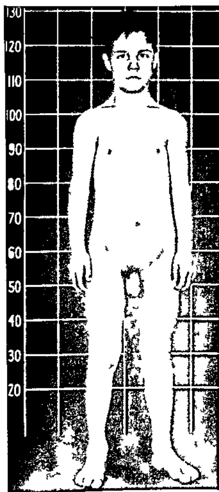


Figure 18 A Virilization associated with an adrenal cortical tumor

has remained well 3 yrs after removal of tumor



Figure 18 D Photomicrograph (x200) of the tumor

Kepler and Keating Cahill and his associates[9, 1] Walters and Sprague[141] and Cleroux and Oppenheim[4] have added a number of cases in which a picture of uncomplicated adrenogenital syndrome in adult women has been associated with an adrenal cortical tumor We have not attempted a review and tabulation of all published cases

Diagnosis Masculinization without the metabolic symptoms usually seen in Cushing s syndrome may occur in adult women as the result of adrenal cortical hyperfunction arrhenoblastomas of the ovary or after prolonged administration of large amounts of androgen (Figure 19 A and B) Adrenal cortical hyperfunction may occur in conjunction with tumor

Arrhenoblastomas of the ovary may be palpable on

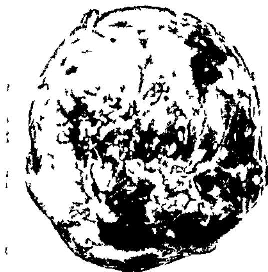


Figure 18 C The tumor in the gross

testes were preadolescent in size and no tumor was palpable within either

Treatment Surgical excision Routes will be discussed below

In the Adult Female

Incidence In a review of the literature prior to 1937 Hugh Young [1] found reports of 24 cases of adrenal cortical tumor in females over the age of 16 years in which surgical excision of the tumor had been performed Unfortunately the histories lacked sufficient detail to permit him to sort them into distinct categories although all were described under the heading The Adreno Genital Syndrome A number most certainly would now be classified as examples of Cushing s syndrome

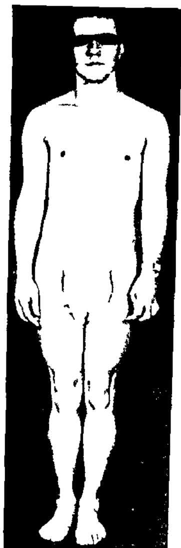
Since Young s review a number of authors including

pelvic examination but when not may confuse the diagnosis Like cases of pure adrenogenital syndrome arrhenoblastomas are almost never associated with the metabolic symptoms usually seen in Cushing s syndrome

As Kepler and Locke[78] have pointed out "pseudo adrenal and quasiadrenal disorders often are the cause of diagnostic worries Simple hirsutism rarely proves to be secondary to an adrenal cortical tumor but when it is associated with obesity and amenorrhea and at times with mild virilism great difficulty may be encountered in establishing the diagnosis All the tools of the endocrinologist may be needed to solve the riddle the true diagnosis may not be established prior to surgical exploration and at times not then even though sections of the adrenal are studied

The following case serves to illustrate the principal diagnostic features of the adrenogenital syndrome in an adult female resulting from an adrenal cortical carcinoma

B C History No 457 100 The Johns Hopkins Hospital a female age 27 years was admitted to the Surgical Service of Dr Mark Ravitch in 1948 complaining of left upper quadrant pain amenorrhea the appearance and growth of hair over the face abdomen and extremities huskiness of voice and a 30 to 40 pound weight loss all of approximately eight months duration Examination revealed a slender woman showing male distribution of pubic and abdominal hair a definite beard a husky voice a small goiter and a large hard rounded left upper quadrant mass The ovaries felt normal on pelvic examination Pyelograms made elsewhere showed a normal left upper urinary tract except for downward displacement of the entire kidney by an extrarenal mass This mass also caused medial displacement of the stomach Chest x rays were negative Blood studies were within normal range Total urinary 17 ketosteroids were 69 3 mg per day the *beta* fraction was not determined Abdominal exploration



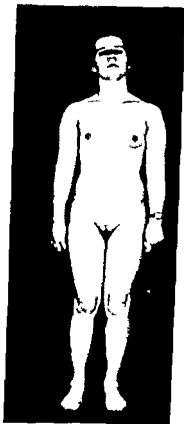


Figure 19 A and B A (*Left*) preoperative appearance of an 18 year old female with adrenogenital syndrome caused by an adrenal cortical adenoma B (*Right*) appearance of patient seven months after removal of the tumor (Courtesy of Dr John E Howard The Johns Hopkins Hospital)

showed downward displacement of the left kidney the total urinary 17 ketosteroids were markedly elevated and the ovaries felt normal There were no metabolic symptoms suggestive of Cushing s syndrome and blood studies were normal

Treatment Provided there is no evidence of metastases surgical excision of the tumor constitutes proper treatment as it does in all cases of adrenal tumor regardless of what type of symptoms are produced

Feminizing Tumors

Hyperadrenocorticism in the male secondary to tumor usually results in Cushing s syndrome Occasionally however isolated expressions of hyperfunction such as feminization may occur without metabolic symptoms

In the Male Child

The only case of an adrenal cortical tumor causing gynecomastia in a male child prior to puberty is that reported by Wilkins[14] some details of which are presented below It will be noted that there is little in the history and examination to suggest feminization other than the pronounced gynecomastia In discussing this case Wilkins points out that gynecomastia is rare between the neonatal period and adolescence and when present suggests a feminizing adrenal tumor In the newborn gynecomastia may result from circulating estrogens produced by the mother and after puberty may be associated with adrenal tumors testicular chorioepitheliomas liver disease Klinefelter s syndrome and following feeding after a period of severe inanition

D G History No A-31153 Harriet Lane Home for Invalid Children of The Johns Hopkins Hospital a boy aged four years and eight months was admitted in 1943 to the Endocrine Service of Dr Lawson Wilkins Dr John

was carried out through a long transverse upper abdominal incision which transected both recti Exposure and removal of a huge 1160 gram tumor was facilitated by resection of three costal cartilages Fifty cubic centimeters of adrenal cortical extract and 5 units of blood were given during operation Postoperative recovery was prompt The tumor on section was an adrenal cortical carcinoma (Figure 20) When last seen in July 1949 15 months after operation her menstrual periods were regular and there was little external evidence of masculinization Her voice was soft and feminine Unfortunately 17 ketosteroid determinations were not repeated

Here again the preoperative diagnosis of a virilizing adrenal cortical tumor was almost certain Masculinization was of recent onset and progressive the pyelograms

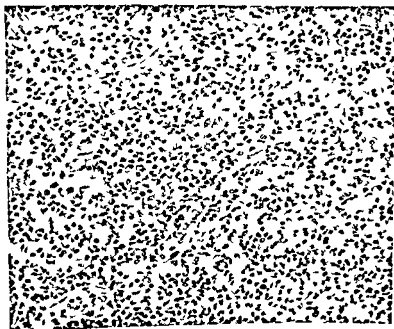


Figure 20 Photomicrograph (x200) of an adrenal cortical carcinoma associated with virilization of an adult female

showed downward displacement of the left kidney the total urinary 17 ketosteroids were markedly elevated and the ovaries felt normal There were no metabolic symptoms suggestive of Cushing s syndrome and blood studies were normal

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Eager Howard had been asked to see the boy previously in the Accident Room because of enlarged breasts Questioning of the mother revealed that she had noted that the boy's breasts first began to enlarge at the age of six months Neonatal hyperplasia of the breasts had not been observed Nothing else unusual had been noted by the mother and growth and development had appeared normal to her His appearance on examination is shown in Figure 21 A Positive findings were a bone age of 10

Age 4 yr 8 mos

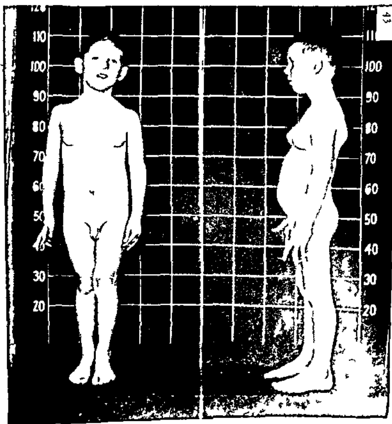


Figure 21 A Feminization associated with an adrenal cortical tumor prior to removal (Courtesy of Dr Lawson Wilkins The Johns Hopkins Hospital)

years marked mammary development some enlargement of the prostate calcification in the region of the right adrenal above a bifid right kidney (Figure 21 C) a slight eosinophilia and a total urinary 17 ketosteroid excretion of 4 1 mg per day Urinary estrogens were slightly increased On exploring the abdomen through a trans

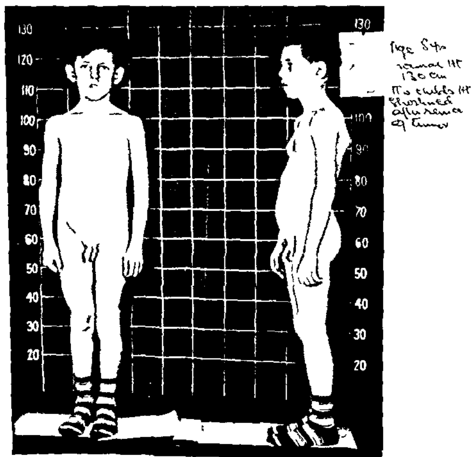


Figure 21 B Appearance of patient three years and three months later (Courtesy of Dr Lawson Wilkins The Johns Hopkins Hospital)



Figure 21 C Intravenous pyelogram showing area of calcification in the tumor above but not displacing a bifid right kidney (Courtesy of Dr Lawson Wilkins The Johns Hopkins Hospital)

verse upper abdominal incision an encapsulated calcified peanut sized tumor could be seen springing from the right adrenal Both the tumor and the right adrenal were removed The left adrenal appeared normal On microscopic examination the tumor appeared to be a benign cortical adenoma thought possibly to arise from the pre

natal zone (Figure 21 D) The only hormonal therapy used was 10 mg DCA on the day of operation and his postoperative course was quite uneventful Figure 21 B is a photograph made three years and two months after operation and shows some residual gynecomastia When last seen in December 1950 the breasts were continuing to regress He was otherwise normal

As stated previously there was little other than gynecomastia to suggest an adrenal tumor in this case The value for urinary 17 ketosteroids though slightly elevated for a boy of this age was not remarkable Furthermore *calcification does not necessarily suggest an adrenal tumor* Strong suspicion plus exploration established the cause

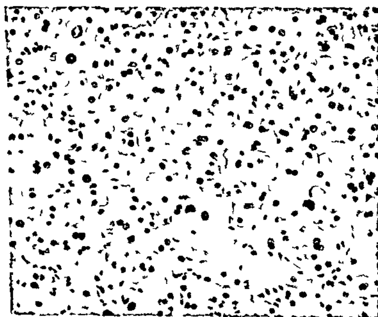


Figure 21 D Photomicrograph (x200) of the benign cortical adenoma removed Patient alive and well eight years after operation (Courtesy of Dr Lawson Wilkins The Johns Hopkins Hospital)

In the Adult Male

Incidence In 1948 when Wilkins[14] reported the feminizing adrenal cortical tumor in the boy described above he also presented a review of feminizing adrenal tumors in males after puberty To 1948 reports of 10 cases were found Adding one previously unreported but studied by one of us (W W S) the total was brought to 11 Armstrong and Simpson[8] added another in 1948 after Wilkins report and in 1951 Mortensen and Murphy[97] added another the thirteenth Recently three additional as yet unreported cases have been brought to our attention[3, 9, 8]

Diagnosis In all cases reported to date gynecomastia has been present and a prominent feature Depression or loss of libido was present in seven cases in the remaining six no information concerning libido is given Atrophy of the testes is recorded in seven as is decrease or loss of sexual hair of male distribution Obesity occurred in two but did not suggest Cushing s syndrome In the majority a palpable abdominal tumor has been present and pyelograms have been of distinct value in localizing the tumor to the adrenal region

Urinary hormonal studies have been made in six cases In two urinary comb growth androgens have been normal and in these same two values for urinary estrogens determined biologically were high In one additional case bioassay showed only a slight increase in urinary estrogen excretion

Unfortunately total urinary 17 ketosteroids were reported in only four cases and the *beta* fraction in only one of these In two elevation of the total is distinct in one less so and in the fourth values are normal In the case studied by one of us total urinary 17 ketosteroids ranged from 196 to 213 mg per day preoperatively and over 95 per cent of this consisted of the *beta* fraction Seventy

milligrams of dehydroisoandrosterone were isolated from one 24 hour specimen of urine

Illustrative Case The following case previously described in part by Wilkins[14] in his review and studied by one of us (W W S) while at the University of Chicago is presented in some detail as it illustrates certain prominent signs and symptoms common to the majority of cases of feminizing adrenal cortical tumors occurring in adult males

G B History No 349 103 The University of Chicago —University Clinics a man aged 42 years was admitted in 1945 to the Endocrine Service of Dr Allan Kenyon and subsequently transferred to the Urologic Service of Dr Charles Huggins Three months before he noted that his breasts had begun to enlarge and shortly thereafter that although his desire for intercourse was strong he was impotent On examination the breasts were enlarged and their areolae pigmented (Figure 22 A) a large mass was palpable in the right upper quadrant and flank and the spleen was enlarged Intravenous pyelograms revealed a large soft tissue mass displacing the right kidney downward (Figure 22 B) No definite pulmonary metastases could be seen on x ray Total 17 ketosteroids ranged from 196 to 213 mg per day preoperatively over 95 per cent of which consisted of the *beta* fraction A Friedman test for urinary gonadotropins was negative Through a transperitoneal incision a 1100 gram tumor was removed (Figure 22 C) which on section (Figure 22 D) proved to be an adenocarcinoma of the adrenal cortex with connective tissue being sarcomatous in nature " During the first week postoperatively both adrenal cortical extract and DCA were used in the management The postoperative course was complicated by symptoms and signs of thrombosis of the inferior vena cava Within one week of operation total urinary 17 ketosteroids had fallen to 14 8 mg per day (Figure 23) with reversion to a normal ratio of *alpha* and *beta* fractions Within five months a

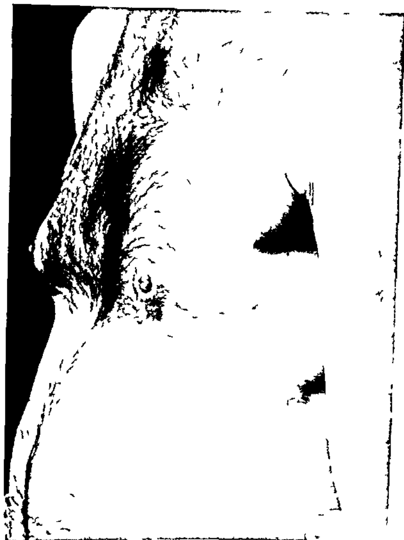


Figure 22 A Feminization associated with an adrenal cortical carcinoma in a male age 42 years

chest x ray (Figure 24) revealed widespread pulmonary metastases and the following month the patient expired



Figure 22 B Intravenous pyelogram showing marked downward displacement and distortion of right kidney by a tumor mass

No urine specimen was obtained prior to the patient's death and hence urinary 17 ketosteroids could not be determined

Treatment and Prognosis Most cases of feminizing adrenal tumors have been far advanced when first seen



Figure 22 C The tumor in the gross (1100 grams)

and consequently prognosis has been poor Only four of the 14 cases occurring in all age groups survived excision of the tumor and were free of metastases at the time they were reported Two of these had not been followed sufficiently long to exclude recurrence

At present surgical excision of the primary tumor prior to metastasis offers the only chance of cure No data is available to permit evaluation of x ray therapy either in conjunction with surgery or alone

In view of the poor prognosis it would seem that for the present early and diligent search for the cause of any and all signs of feminization should offer men with tumor a better chance Certainly this search should include determination of the urinary 17 ketosteroids

Hormonally Active Medullary Tumors

Incidence

Pheochromocytoma Pick[168] in 1912 first suggested the term pheochromocytoma" for tumors of the adrenal

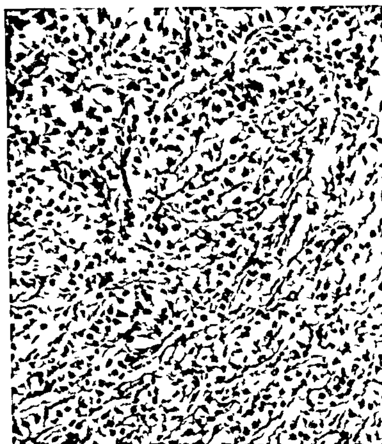


Figure 22 D Photomicrograph (x200) of tumor showing "sarcomatous nature

medulla reserving the term paraganglioma for chromaffin tumors in locations outside the adrenal and its immediate vicinity Ten years later Labbe Tinel and Doumer [81] reported the first case of paroxysmal hypertension due to a tumor of the adrenal medulla and in 1926 *Vaquez and Donzelot* [13] *appear to have made the first* diagnosis of a pheochromocytoma in the living subject According to Howard and Barker [6] "The first report of

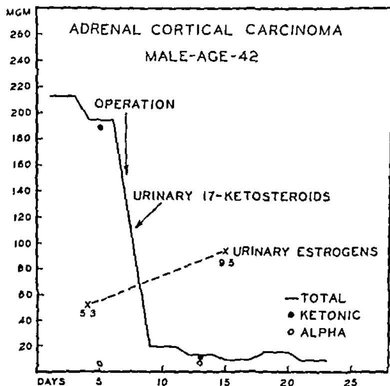


Figure 23. Urinary 17-ketosteroids and estrogens before and after removal of an adrenal cortical carcinoma associated with feminization in an adult male. 17-ketosteroids are expressed in milligrams per day; urinary estrogens in microgram equivalents of *alpha* estradiol benzoate per day. Note that prior to operation almost all of the total ketonic fraction was composed of *beta* 17-ketosteroids. Thereafter there was a reversion to a normal ratio of *alpha* and *beta* fractions. (Previously reproduced by Huggins and Bergenstal.[64])

an operative removal of such a tumor with relief of symptoms was made by C. H. Mayo.[3] The tumor was described in his article as a retroperitoneal malignant blastoma. After further cases with similar symptoms had been reported, however, the sections were reviewed and the diagnosis changed to pheochromocytoma.[119] Actually, the first



Figure 24 Pulmonary metastases secondary to an adrenal cortical carcinoma associated with feminization in an adult male (Refer to Figures 22 A B C and D)

report of a successful operation for this type of tumor that we have found was published by Roux [117] in February 1926 From the very brief description of the symptoms in his patient we feel quite sure that paroxysmal hyper tension was present but no blood pressure determinations are given The combination of correct preoperative diag nosis and successful surgical removal of a pheochromo

cytoma with paroxysmal hypertension was first achieved by Pincoffs[107] and Shipley[1 3]

Although a pheochromocytoma is a comparatively rare tumor over 200 cases have been reported to date Having been observed with equal frequency in the male and female it occurs usually between the ages of 20 and 50 years though the extremes of seven and 71 are reported According to Brines and Jennings[16] almost 90 per cent of these tumors are in the adrenal with a slight but definite predilection for the right side In Cahill's[1] series of 15 cases involving 17 tumors seven were located outside the adrenal one of which was in the neck Phillips[105] has reported an occurrence of this tumor in the thorax

Calkins and Howard[4] were able to find 15 patients with bilateral tumors five of which were malignant In this report they present two most interesting cases of bilateral tumors studied by them and operated by Colston occurring in blood relations aunt and niece Of further interest was the history that the latter's mother and former's sister had died at age 28 of paroxysmal hypertension The niece has died of metastases since this report Sprague *et al*[1 0] estimate that these tumors are bilateral in at least 10 per cent of cases and that they may be malignant in perhaps 10 per cent Karsner[77] estimates malignancy as being of the order of 8 per cent Ten cases have been reported as occurring in the organs of Zuckerkandl – those small nests of paraganglion cells associated with the sympathetic plexuses and located along the aorta near the root of the inferior mesenteric artery (Yarborough[155])

Diagnosis

Symptomatology There appears to be little question but what the symptoms associated with pheochromocytomas are secondary to release into the blood stream of

epinephrine or norepinephrine However from a review of the symptoms in proved cases it appears likely that no constant pattern is observed but rather several patterns seemingly dependent on which vasopressor substance is released in what quantities and whether intermittently or continuously Thus tumors have been found in the following types of cases (1) those in which no symptoms have been elicited and in whom a tumor is found at autopsy (2) those in which there are characteristic reproducible paroxysms of hypertension and associated symptoms and (3) those in whom the chief symptom or finding is sustained hypertension simulating either the essential or malignant type

Cases of true pheochromocytoma without cardiovascular symptoms or signs are distinctly in the minority probably representing less than 10 per cent of all In a recent report of five cases of pheochromocytomas unsuspected prior to autopsy Berkheiser and Rappoport[1] review the histories in some detail Mild to moderate hypertension was present in four of the five only one presenting no signs or symptoms of a cardiovascular nature At autopsy two days after a combined abdominoperineal resection for a carcinoma of the rectum a 4 cm pheochromocytoma of the left adrenal was found In addition multiple neurofibromas were present as well as liver metastases histologically like the primary rectal tumor

Characteristically pheochromocytomas give rise to paroxysms of hypertension accompanied by anxiety headache precordial and epigastric distress palpitation sweating pallor coldness of the extremities and nausea or vomiting Roughly one third to one half of patients with these tumors have attacks of this general pattern varying somewhat from patient to patient and in degree However this varies for in a series of 25 patients studied by Sprague Kvale and Priestley[1,8] the tumors of 14 were

considered to be functioning paroxysmally. According to Wells and Bowman[143] the incidence of chronic hypertension in patients with functioning tumors increases with time. This appears logical as commonly it has been observed that as the disease progresses the interval between attacks becomes shorter and shorter.

Paroxysmal attacks secondary to pheochromocytoma must be differentiated from severe anxiety attacks. This may be difficult. In a review of 12 cases seen at The Johns Hopkins Hospital Howard[61] was impressed that whereas at times a paroxysm appeared to be precipitated by anxiety or exertion, more frequently manipulations causing pressure on the tumor or metabolic changes such as hypoglycemia appeared responsible. Furthermore, most patients with tumors were emotionally stable. At times an indescribable aura preceded a paroxysm and always precordial pain followed rather than preceded the hypertension. Smithwick *et al*[125] have been impressed with the frequency with which all patients with tumors, whether associated with persistent or paroxysmal hypertension, manifest other pharmacological effects of epinephrine release. Howard's experience is similar in that over half of his patients perspired almost continuously, several had rapid pulse and a low grade fever, and one third had basal metabolic rates greater than +15. Although diabetes occurred in two patients with pheochromocytomas and was relieved by removal of the tumor, he was not impressed with the frequency of association of the two conditions, believing that hypertension and diabetes were more apt to occur as a coincidence.

As noted above, the majority of patients with pheochromocytomas do not have paroxysms but present themselves with clinical pictures indistinguishable from that of essential or malignant hypertension. As a consequence, pharmacological means have to be used to differentiate

these diseases. In Smithwick's[115] series of 1,000 cases of hypertension subjected to lumbodorsal sympathectomy, exploration of both adrenals at the time revealed five pheochromocytomas (0.5 per cent).

Pharmacologic Tests. In general these are of two types: (1) those designed to stimulate discharge of pressor compounds from the tumor and (2) those designed to lower blood pressure by competitive inhibition of the pressor compounds released by the tumor. In general these aids have been of great help.

The histamine test introduced by Roth and Kvale[116] in 1945 belongs to the first group — those agents which stimulate discharge of pressor compounds from the tumor — and hence mimic a paroxysmal attack. It has been the experience of many that this test has been most useful in establishing the cause of paroxysmal hypertension, whereas in patients with sustained hypertension competitive drugs such as benzodioxan, etc., are preferred.

It should be emphasized from the start that *a negative histamine test does not rule out the presence of a pheochromocytoma.* Care in conducting the test reduces the number of false negatives to a very few. Of a consequence it becomes important to heed the recent admonitions of Dr. Grace Roth,[115] who has had the most experience with this test. Prior to the test the patient should not have had any sedation for a minimum period of 12 hours; he should not have had any thiocyanate for four to six days or until thiocyanate can no longer be detected in the blood; a cold pressor test should be performed.

Important in conducting the test itself are the size of the dose, the way the drug is administered, and the frequency of determination of the blood pressure after administration of the drug. Roth stresses that small doses of histamine increase the margin of safety and suffice to stimulate an attack. Thus she recommends a dosage of

0 01 to 0 05 mg histamine base intravenously, but never more It is best administered through one of the ports of a three way stopcock while a slow intravenous infusion of saline is running to avoid the possible effect of veni puncture on the blood pressure

After giving the drug intravenously to a patient with a pheochromocytoma and if blood pressure determinations are made with sufficient rapidity within 30 seconds there is a fall in blood pressure Immediately thereafter the blood pressure rises and reaches a peak within one to three minutes This rise exceeds by some 100 mm the elevation initially obtained by the cold pressor test Such is not the case in normal individuals hyper reactors to the cold pressor test nor those with established hypertension Often in hypertensives with a labile blood pressure the elevation in blood pressure may be greater in four to ten minutes after injection than at two minutes Figure 25 illustrates a typical positive histamine test in a patient with paroxysmal hypertension in whom a pheochromocytoma was removed by one of us (W WS) Her blood pressure response to cold is shown for comparison (This woman's case history is described in detail elsewhere by Dr Robert E Mason[9] being one of two in which negative benzodioxan tests were observed but in both of which histamine tests were positive)

Some internists have criticized the histamine test not only on the basis of the several false negative reactions observed but because of violent hyper reaction with the possibility of a cerebral accident pulmonary edema or an ocular hemorrhage It is the feeling of Howard[11] and the authors that in the presence of persistent hypertension with obvious vascular damage the histamine test is best omitted but in patients with paroxysmal hypertension who are normotensive between attacks the test gives much reliable information and no more danger will result

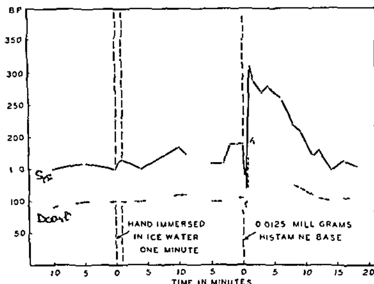


Figure 25 Cold pressor and histamine tests prior to removal of a pheochromocytoma Tests were done in succession on the same day Note that maximum systolic pressure after histamine exceeds that following cold by more than 100 mm mercury

from a histamine induced paroxysm than one occurring spontaneously

Other agents belonging to the group which stimulate an attack include etamon® (tetraethylammonium) and mecholyl® Neither has proved as satisfactory as histamine

As stated above in the determination of the cause of persistent hypertension drugs which act as competitive inhibitors of the pressor compounds released by the tumor are to be preferred Three examples of such drugs are benzodioxan dibenamine hydrochloride and regitine®

In 1947 Goldenberg Snyder and Aranow [43] introduced the use of 2 (1 piperidylmethyl) 1 4 benzodioxan (piperoxan 933 Fourneau or benodaine®) in the diagnosis of

0.01 to 0.05 mg histamine base intravenously, but never more. It is best administered through one of the ports of a three way stopcock while a slow intravenous infusion of saline is running to avoid the possible effect of venipuncture on the blood pressure.

After giving the drug intravenously to a patient with a pheochromocytoma and if blood pressure determinations are made with sufficient rapidity, within 30 seconds there is a fall in blood pressure. Immediately thereafter the blood pressure rises and reaches a peak within one to three minutes. This rise exceeds by some 100 mm the elevation initially obtained by the cold pressor test. Such is not the case in normal individuals, hyperreactors to the cold pressor test nor those with established hypertension. Often in hypertensives with a labile blood pressure the elevation in blood pressure may be greater in four to ten minutes after injection than at two minutes. Figure 25 illustrates a typical positive histamine test in a patient with paroxysmal hypertension in whom a pheochromocytoma was removed by one of us (W W S). Her blood pressure response to cold is shown for comparison. (This woman's case history is described in detail elsewhere by Dr Robert E Mason,[9] being one of two in which negative benzodioxan tests were observed but in both of which histamine tests were positive.)

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longer Three to five days are required for full recovery from a single injection during which time it is impossible to counteract its action with epinephrine Its recommended test dose is 7 mg for each kilogram of body weight dissolved in 300 cc of 5 per cent dextrose and given intravenously over the course of one hour Because of the frequency of untoward side reactions and false positive tests in patients with essential hypertension few recommend its use for the differential diagnosis of pheochromocytomas

In 1951 Grimson and his associates[3] reported their experiences with regitine® (2 (N p tolyl N (m hydroxyphenyl) aminomethyl) imidazoline hydrochloride) as a routine testing agent for pheochromocytoma in patients with hypertension a single intramuscular injection of 5 mg serving as the test dose In patients with proved tumors regitine® produced a reduction of blood pressure which lasted longer than that produced by benzodioxan and in addition was associated with fewer side effects and with less fluctuation in blood pressure in patients with hypertensive vascular disease As noted above it appeared to offer no advantage over benzodioxan in overcoming the false positive tests so frequently observed in uremia although no false negative tests have been encountered to date As yet we have had no experience with the drug

Roentgenologic Aids Numerous radiologic technics have been introduced to aid in preoperative localization of the tumor once the diagnosis has been established by symptomatology and pharmacologic tests These have included perirenal insufflation with air or oxygen laminography and aortography Whereas it is always gratifying to have a nice preoperative film demonstrating a tumor it has always seemed to us that this is of little importance

pheochromocytomas associated with persistent hypertension This drug appears to be a true competitor of epinephrine and norepinephrine although some question competitive action with the latter

This test is carried out in a similar fashion to that described for histamine However according to Howard barbiturates do not interfere with the test Following intravenous administration of the currently recommended test dose of piperoxan over a two minute period (15 mg total or 0 25 mg for each kilogram of body weight), the blood pressure is carefully recorded and the over all response of the patient noted A positive response indicating the probable presence of a pheochromocytoma consists in a significant drop in both systolic and diastolic blood pressures starting within two to three minutes after injection and returning to control levels within 20 minutes *Not all patients with persistent hypertension due to a proved pheochromocytoma give positive tests* In the series studied by Goldenberg and his associates [4] Fifty nine patients with operatively demonstrated pheochromocytomas have shown positive benzodioxan tests while only three false negative tests have been observed Others including Calkins Dana and Howard Place [104] and Meilman have observed false negative tests

False positive tests may also occur Grimson and his associates [10] in a recent paper which dealt with the comparative merits of benzodioxan and regitine [9] found that both drugs gave false positive values in 5 of 11 patients with hypertensive vascular disease and uremia

Dibenamine hydrochloride (N dibenzyl *beta* chloroethylamine hydrochloride) has also been used successfully as a test for pheochromocytoma in patients with persistent hypertension Like benzodioxan it appears to be an epinephrine competitor but one which acts much



Figure 26 Percutaneous aortogram demonstrating pheochromocytoma of right adrenal (method of Peirce [104]) (Courtesy of Dr Elmer Belt and Dr Willard E Goodwin University of California at Los Angeles)

particularly in view of our belief that transperitoneal exploration of both adrenals and periaortic ganglia should be carried out in every case in which pheochromocytoma is suspected In three recent cases of pheochromocytomas seen at The Johns Hopkins Hospital the tumors were correctly localized with laminograms This technic however could not be expected to reveal small extra adrenal tumors

Although we have made a number of aortograms for other purposes we have not used this technic in cases of suspected pheochromocytoma Recently we were unable to demonstrate a 4 cm adrenal cortical tumor by percutaneous aortography Most recently however my former associate Dr Willard E Goodwin now in charge of Urology at the University of California at Los Angeles sent me serial aortograms which he and Dr Elmer Belt had made preoperatively according to the percutaneous method of Peirce [104] in a boy with a pheochromocytoma which at operation replaced the right adrenal Through their courtesy one of the postinjection films showing excellent localization of the tumor is reproduced in Figure 26 No untoward side effects were noted in this patient nor have we experienced any in our rather large series done for other purposes

Examination of the Urine In a recent communication A Engel and U S von Euler [37] report greatly increased urinary excretion of norepinephrine epinephrine in two cases of proved pheochromocytoma in which these determinations were made Of further interest was the observation that the proportions of both pressor substances were approximately the same as in the tumors removed After the removal of the tumors the norepinephrine epinephrine output in the urine fell quickly to normal in both cases It is hoped that this highly exciting work will be extended

equivocal a histamine test reproduced in all details one of the spontaneous attacks described with the blood pressure rising to over 300 mm systolic over 190 diastolic after a transient fall This rise exceeded by much more than 100 mm the elevation obtained by a cold pressor test An intravenous pyelogram was unsatisfactory but a laminogram suggested a small mass above the left kidney A diagnosis of a pheochromocytoma causing paroxysmal and sustained hypertension was made and shortly thereafter one of us (W W S) carried out exploration of the adrenals through an upper transverse abdominal incision The right adrenal was normal the left adrenal was involved in tumor This tumor measured 4 centimeters in diameter was reddish brown in color and seemed to be fused with a normal appearing gland which necessitated partial adrenalectomy to insure removal of all of the tumor After removal of the tumor and for the next 24 hours her blood pressure was maintained with dilute epinephrine solution (1 milligram per 100 cubic centimeters of fluid) at 120/80 to 140/100 regulating the rate of flow according to the blood pressure In all during this period she received 22 milligrams Convalescence thereafter was essentially uneventful Histamine and benzodioxan tests done on the tenth postoperative day gave normal pressure responses She was discharged on the following day and has remained well to date

Medullary Tumors with No Recognizable Hormonal Activity

Neuroblastoma (Sympathicogonioma and Sympathicoblastoma)

Incidence Whereas incidence figures are to be found in the literature for neuroblastomas no data can be found giving the incidence of sympathicogoniomas and sympathicoblastomas individually Generally the suffix blastoma is used to indicate a more *malignant tumor but*

Illustrative Case

E G History No 527036 The Johns Hopkins Hospital a housewife aged 28 years was admitted in 1950 to the Medical Service of Dr E C Andrus with the complaints of high blood pressure and albumin in the urine She recalled that at age 14 her blood pressure was 140 and on admission to college was 160/100 remaining at that level until 1949 In the spring of 1947 she began to experience rather frequent severe headaches which were associated with profuse perspiration These headaches would come on at any time of day would last about an hour and spontaneously go away She became pregnant late in 1948 or early 1949 and in September 1949 delivered spontaneously a full term living male child Several blood pressure readings ranged close to 180/110 and 2 plus albumin was found on repeated urine examinations On discharge eight days postpartum her blood pressure was 145/110 Inquiry revealed that in the third trimester of her pregnancy the character of her headaches had changed These would begin with a sense of nausea in the pit of her stomach and a feeling of malaise with mild joint aches Shortly thereafter she would experience severe aching pain in the occipital part of her head with radiation to both frontal areas These were described as steady and crushing in character and were associated with pounding of her heart as if it were too large for my chest Her face would blanch and she would perspire profusely These attacks appeared to come on more frequently when she was hungry would last for about an hour and when gone would leave her feeling fine Daily blood pressure examinations after admission to The Johns Hopkins Hospital showed wide fluctuations ranging from over 300 to as low as 140/90 She was observed to suffer attacks similar to those described in the history with nausea followed immediately by flushing and palpitation aching of the joints dyspnea sweating and blood pressure elevation to over 300 Whereas a benzodioxan test was

tal system As a result symptoms vary from case to case As in Wilms tumor frequently no symptoms occur and the infant is brought to the physician because the mother has felt an abdominal mass As the tumor grows and metastasizes multiple symptoms occur which depend upon involvement of nearby structures the site of distant metastasis and the ability of the child to express his feelings Frequently the infant shows evidence of wasting Diarrhea or constipation jaundice anemia and generalized toxemia are usually secondary to extensive liver involvement

In the three cases from which we have drawn illustrative material (Figures 27 through 33) in the first attention was directed to the tumor by the mother feeling an abdominal mass in the second the physician palpating the tumor while examining the infant for upper respiratory infection and in the third when the parents sought medical attention for their 4½ year old



Figure 27 Postoperative appearance of a 17 month old girl following surgical excision of a sympathicogonioma Excision preceded by x ray therapy resulting in an estimated 50 per cent decrease in the size of the tumor mass Outcome fatal

Karsner[73] uses the term to indicate a higher degree of differentiation than is true of the sympathicogonioma Furthermore he states Practically the sympathicoblastoma is less malignant than the sympathicogonioma especially when it occurs in later periods of life

Occurring with equal frequency in either sex and in or near either adrenal these tumors are found almost entirely in young children some 80 per cent within the first five years of life Those occurring in the older group are usually less malignant and most often are sympathicoblastomas Neuroblastomas are the most common sympathetic tumors in childhood and to date approximately *400 cases have been reported an incidence quite like that* of Wilms tumor of the kidney Whereas they usually are unilateral bilateral tumors have been observed

Until recently distinction was made between Pepper and Hutchison types the former referring to neuroblastomas of the right adrenal principally metastatic to the liver the latter including tumors of similar histology arising in the left adrenal principally metastatic to the skull However analysis of cases by Farber[38] Karsner and others[130] has shown that the distribution of the metastases *is not determined by the histologic character or the ana*tomic site of the original tumor Hence these eponymic designations are not justified Wittenborg[illegible] studying 73 cases of neuroblastoma observed that the upper abdomen *was the primary site of the tumor in 74 per cent* some 60 per cent had metastasized at the time of diagnosis

Diagnosis

Symptoms Usually attention is directed to a neuroblastoma by the presence of a painless nontender abdominal mass or because of metastases to the liver or skele

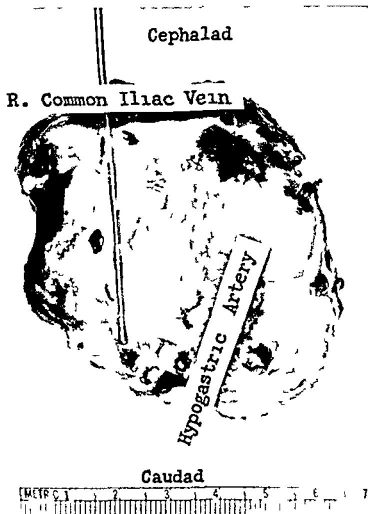


Figure 29 A A gross appearance of a sympathicogonioma which in order to be removed required resection of portions of the right hypogastric artery and right common iliac vein B photomicrograph (x200) of the tumor showing rosette formation characteristic of sympathicogoniomas (Courtesy of Dr Richard Kieffer and Dr Glenn Morrow The Johns Hopkins Hospital)



Figure 28 Gross appearance of sympathicogonioma (Refer to Figure 27.)

son shortly after he had complained of abdominal pain and they had noticed a lump on his head which had increased in size and was associated with a "blood shot eye as if a blood vessel had burst."

Signs The presence of an abdominal mass on physical

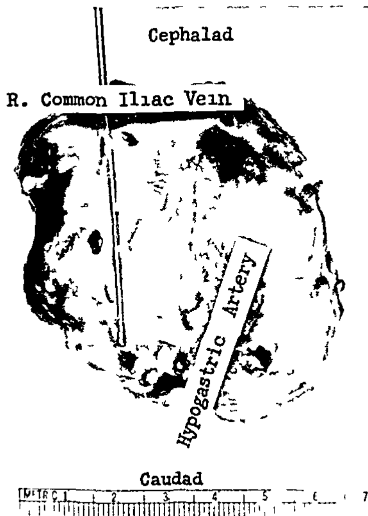


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examination of an infant or young child immediately suggests a neuroblastoma or a Wilms tumor of the kidney Skeletal x rays and excretory urograms often establish the diagnosis Whereas skeletal metastases are quite common in neuroblastoma they are rare in Wilms tumors Although a neuroblastoma may invade the kidney and present a pyelogram which suggests a renal embryoma

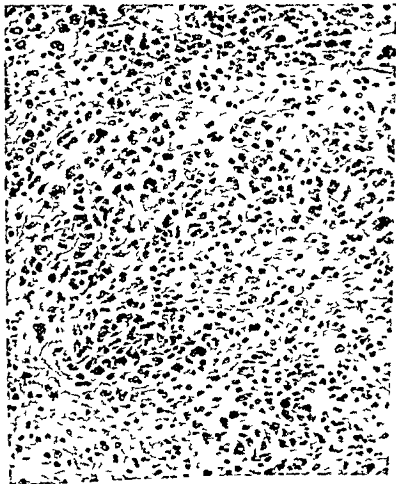


Figure 29 B



Figure 30 A. A preoperative intravenous pyelogram in a patient with a pelvic sympathicogonioma. (Refer to Figures 29 A and B.) Note pronounced lateral displacement of both ureters, right hydroureteronephrosis and left hydroureter. B, intravenous pyelogram in same patient six months after removal of tumor. The course of both ureters is straight and only slight caliectasis and pyelectasis persist on the right.

this is unusual Most frequently neuroblastomas appear as extrarenal masses displacing the kidney downward when arising in the adrenal or causing lateral displacement of the ureters when arising lower in the abdomen with pyelographic signs of back pressure when large enough to obstruct (Figure 30 A) At times both neuro



Figure 30 B

blastomas and renal embryomas are calcified (Figure 32)

Neuroblastomas are distinguished from hormonally active tumors by the absence of symptoms and signs suggestive of adrenal cortical or medullary secretion as outlined previously Wilkins[146] however has observed a 7½ year old girl with a tumor which resembled a neuroblastoma who clinically had severe hypertension and whose benzodioxan test was positive Upon staining the fresh tumor tissue with ferric chloride the chromaffin reaction was not seen and on assay only a minute amount of epinephrine was obtained

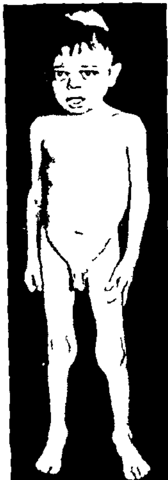


Figure 31 Pathetic appearance of a boy age one and one half years secondary to disseminated neuroblastoma Biopsy of scalp lesion was positive for neuroblastoma Transient improvement followed each course of nitrogen mustard but death occurred three weeks after last course (Courtesy of the Department of Pediatrics The Johns Hopkins Hospital)

Diagnosis is established by biopsy either aspiration or surgical of the tumor or a metastasis

Treatment

It appears that physicians associated with The Children s Medical Center in Boston have had the greatest experience in the treatment of neuroblastomas and the inter

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Figure 30 B

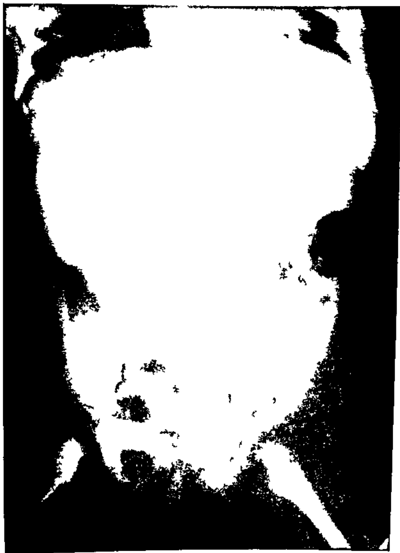


Figure 32 Calcified mass in right upper quadrant representing the primary tumor in a patient with a disseminated neuroblastoma." (Refer to Figure 31.)

ested reader is referred to the original papers of Farber[38] Wyatt and Farber[14] and Wittenborg[19] of that institution for details The latest communication by Wittenborg (1950) reviews in detail 73 cases subjected to no specific treatment surgery alone or surgery and postoperative roentgen therapy and to this we wish to refer

In the group of 28 cases in which no specific therapy was carried out 20 had metastases when first seen all died within one year The remaining eight when first seen appeared to have localized tumors Of these three died within 12 months of local or distant spread one died with metastases 10 years after the diagnosis two were discovered incidentally at autopsy and two are alive and well 12 and 16 years after diagnostic biopsy

In 12 therapy consisted of surgical excision of the primary tumor only Seven (58 per cent) survived three years or more Six of seven in whom the primary tumor appeared to be localized to the abdomen survived three years or more a survival rate of 85 per cent for this particular group

Eleven patients received x ray therapy after surgery but not before Two with skeletal metastases at the time postoperative therapy was begun died within 18 months Nine tumors appeared to be localized after preoperative study and at surgery In three of these the surgeon felt that excision was complete in six tumor tissue was known to have been cut across and part left behind Four in the latter group (60 per cent) are living and well having been followed three to nine years

Twenty two patients underwent biopsy only followed by x ray therapy One died within one week after treatment was begun Six of the remaining 21 patients with metastases are living and well three to 12½ years after x ray therapy (27 per cent) The remaining 15 patients

with metastases all died within the year after biopsy and initiation of x ray therapy

Wittenborg concludes that early detection and complete surgical excision of the apparent local tumor offers the best prognosis However if no distant metastases can be demonstrated and surgical excision is incomplete x ray therapy still offers a good prognosis Furthermore "primary neuroblastoma in the abdomen with metastases to the liver however still offers an excellent prognosis if treated by irradiation A 100 per cent three year survival in this group of six patients is reported

For a detailed discussion of the technic of roentgen therapy in these cases the radiotherapist should consult Wittenborg s original articl Of particular interest to one who is not a radiologist were Wittenborg s observations supporting immediate postoperative therapy without waiting for complete healing of the incision No wounds broke down

At this writing no reports are available to aid in assessing the value of radioactive drugs nitrogen mustard or anti folic acid compounds in the treatment of disseminated neuroblastoma However Wittenborg[10] calls attention to a forthcoming report of 21 patients so treated by Dr Sidney Farber and associates Department of Pathology The Children s Medical Center Boston

In concluding this discussion of neuroblastomas the following case is presented which illustrates many of the features involved in diagnosis and treatment

R D History No A 84846 Harriet Lane Home for Invalid Children of The Johns Hopkins Hospital a boy aged one year and three months was apparently well until three months prior to entry here The child was taken to the family physician because of a cold and on physical examination a large mid abdominal mass was

felt Intravenous pyelograms revealed that this mass had caused marked lateral displacement of both ureters right hydroureteronephrosis and left hydroureter (Figure 30 A) At exploratory laparotomy elsewhere the tumor was judged to be inoperable A biopsy revealed a "neuro blastoma" The patient was referred here for x ray treat ment Following two courses of nitrogen mustard therapy judged to be ineffective the patient was again explored (Drs R Kieffer and G Morrow) and by resecting por tions of the right hypogastric artery and right common iliac vein it was possible to remove the tumor apparently intact Figure 29 A shows the operative specimen and Fig ure 29 B a section from it Postoperative convalescence was quite uneventful and within two weeks x ray therapy was begun The pretreatment factors were 250 KVP 15 MZ 5 cu 1 al 50 STD 1 7 hvl calculated to deliver 3000 r D During a period of approximately two months the child received 49 treatments equally divided between two ports This resulted in a final tumor dose of 2600 r to the midplane of the abdomen Because the hema topoietic system would not tolerate higher daily doses than 50 to 75 r per day per one field a shorter course with larger daily doses as suggested by Wittenborg [10] was out of the question

At this writing over six months since operation the child is living and well Intravenous pyelograms reveal good kidney function right and left with only slight caliectasis and pyelectasis (Figure 30 B) The course of both ureters is straight Bone and chest films reveal no metastases

Ganglioneuroma As stated at the beginning of this chapter Stout [illegible] divides ganglioneuromas into two groups (1) those that are well differentiated and usually benign and (2) those that are incompletely differentiated and rather often malignant

Benign Ganglioneuroma

Incidence McFarland and Sappington[94] in a review of the literature in 1935 found records of 143 cases Occurring more commonly in females than males over one half have been reported in patients under 20 years of age However they may occur at any age Frequently they are an incidental autopsy finding Located most frequently in the posterior mediastinum they also occur in the paravertebral sympathetic ganglia and in the adrenal medulla Over 80 per cent of all ganglioneuromas are benign

Gross and Microscopic Appearance Benign ganglioneuromas are round to oval in shape grayish white on cross section fairly well encapsulated and although at times they reach huge dimensions do not invade locally or metastasize Derived from mature sympathetic nerve cells these tumors are composed of mature ganglion cells intermixed with countless nerve fibrils which are twisted and irregular in appearance and without connection with an end organ (Figure 33) Characteristically the ganglion cells are large round to oval in shape and contain one or two round nuclei with prominent nucleoli Cytoplasmic processes may be prominent and at times the nerve sheaths may show microcystic changes

Symptoms Benign ganglioneuromas are usually silent but may give rise to signs and symptoms as a result of their interference with local functions by means of the pressure caused by the expanding growth

Treatment Surgical excision if necessary

Malignant Ganglioneuroma

Stout[1,2] reports that about one fourth of all ganglioneuromas are incompletely differentiated These he divided into two groups "In one the ganglion cells of the

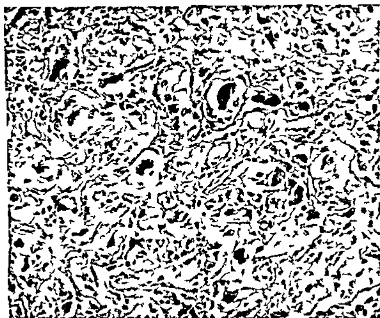


Figure 33 Photomicrograph (x200) of a benign ganglioneuroma in this instance an incidental autopsy finding (See text for description of histology)

entire tumor shows a mixture of cells varying from undifferentiated sympathicoblasts up to fully or incompletely differentiated ganglioneuroma while another contiguous portion will be a characteristic sympathicoblastoma Of this type 65 per cent produce metastases"

Removal of the tumor is the treatment provided there is no clinical evidence of metastases Karsner [3] states There is no proof that irradiation is curative

VI

SURGICAL TREATMENT OF ADRENAL TUMORS

(*Excluding Cushing's Syndrome*)

SURGICAL ROUTES

SINCE GORDON HOLMES [7] first successfully removed an adrenal cortical tumor in 1924 and Charles Mayo in 1927 [93] removed what proved to be a pheochromocytoma numerous surgical approaches to the adrenal have been proposed These include every conceivable route

Thus Crile [8] (1932) denervating the adrenals "made the approach along the lumbar back muscles through a vertical incision Later he used a modified kidney incision This modified kidney incision ran from behind forward immediately beneath and to the midportion of the twelfth rib where it turned and was carried vertically downward Koster *et al* [9] (1931) advocated an incision extending from the tip of the twelfth rib obliquely to the anterior superior spine down through the muscle wall and fascia to the perirenal fat Prior to adrenal exploration they opened the peritoneal cavity and explored the pelvis Broster and Vines [1] (1933) in performing unilateral adrenalectomy for female pseudohermaphroditism with congenital adrenal hyperplasia employed the transthoracic approach Walters [141] (1934) in dealing with tumors used a lateral posterior lumbar incision—similar to that used in approaching the kidney Cahill [19] (1936) operating for adrenal cortical tumors recommended an "oblique incision (beginning) at the ensiform and ex

tended along the costal flare until adequate exposure was obtained—exposure (was) facilitated by use of an elevated bridge on the table situated so that the costal flare is opened and the subcostal area projected forward" Young[106] (1936) advocated simultaneous exposure of the adrenals through posterior verticolateral incisions and devised a special self retaining retractor to aid in the procedure Zintel *et al*[111] (1951) in performing subtotal ("95 per cent") adrenalectomy for hypertension recommend exposure of the adrenal "through a lateral subcostal incision with the patient in the lateral decubitus position and the kidney rest or kidney bar of the operating table three inches cephalad to the lowest point of the costal margin" They found it unnecessary to resect the twelfth rib Huggins and Bergenstal[64] (1951) performing bilateral adrenalectomy in patients with disseminated cancer who relapsed some time after orchiectomy and estrogen therapy "find that the posterolateral approach gives incomparably the best exposure—An incision 20 to 25 cm long is made in the loin over the 12th rib which is resected the fascia of Gerota is incised" Earlier Huggins and Scott[69] (1945) used a similar incision without rib resection Crimson[48] (1951) has most recently advocated a transthoracic and transdiaphragmatic approach which "permits palpation of the abdominal content through an incision in the left diaphragm"

That the exposure and removal of a localized adrenal tumor at times is difficult is not denied no matter what the surgical approach In our experience no one approach is suitable for dealing with all types of adrenal pathology Though some will disagree the following suggestions based on our experience are offered

Pheochromocytoma

Once the diagnosis of a pheochromocytoma has been made on clinical grounds it is established on finding a

tumor at exploration Treatment is clearly surgical removal of the tumor Two important considerations are 1) which approach to use and 2) how to manage the patient during and after operation

Because it has been amply demonstrated that pheochromocytomas may arise in both adrenals outside the adrenal in its immediate vicinity and along the aorta and sympathetic chain all these regions must be explored We believe that this is best accomplished through a transverse upper abdominal incision which transects both recti The procedure is best carried out under general anesthesia using ether administered through an endotracheal tube

Customarily we expose the left adrenal first mobilizing the spleen medially and the kidney inferiorly Four broad Deaver retractors whose blades are protected with Mikulicz pads serve admirably in exposing the posterior peritoneum above the kidney and anterior to the adrenal After incising the peritoneum the tumor or adrenal which may have been palpable on approaching this area usually presents itself The blood supply cannot be defined for tumor as it can for the majority of normal adrenals Preliminary to removal of a tumor whether it is a part of or distinct from the left adrenal the right adrenal area is explored retracting the liver upward the intestines medially the kidney downward and the lateral belly wall outward again with four broad Deaver retractors

If only one tumor is found and it is in such close association with one adrenal as to make it impossible or unwise to remove only the tumor both the tumor and the adrenal are removed provided the opposite adrenal is grossly normal If both adrenals are involved partial resection of the adherent normal gland may have to be done although in such cases the risks of recurrence of tumor and adrenal insufficiency are great

Subsequent to exploration of both adrenal areas the

entire abdomen should be explored generally beginning in the region of the periaortic sympathetic ganglionic chain Furthermore it is important to recall that tumors have been reported to have occurred in the thorax and neck Consequently it is wise to check all patients post operatively with pharmacologic tests to determine if all tumors have been removed

Adrenal Cortical Tumors

Whereas we agree with Priestley *et al* [111] that if Cushing s syndrome is secondary to an adrenal cortical tumor the contralateral gland frequently appears atrophic we have never observed atrophy of the adrenal on the side opposite to a cortical tumor which had resulted in virilization or feminization Consequently in the latter group we see little need of exploring both sides if the tumor has been localized preoperatively The selection of the surgical route will depend largely on which approach we feel will give us best exposure whether it is transthoracic transperitoneal or lumbar We have used them all A good illustration of how one must modify the approach to suit the particular case is that of a 4½ year old boy with uncomplicated adrenogenital syndrome treated in The Johns Hopkins Hospital in 1948 and again in 1949 the details of which are published [147] Preoperative pyelograms demonstrated a very large calcified mass in the region of the right lobe of the liver which had caused little if any distortion of the right kidney (Figure 34) Transperitoneal exploration of this mass by one of us (W W S) revealed that it was entirely embedded in the right lobe of the liver and that if the tumor were to be removed in its entirety one would have to resect the major share of this portion of the liver The operation was terminated without attempting this However one year later Dr Ravitch and one of us operated again through a transverse right



Figure 54 Plain film of abdomen showing calcified area in right lobe of liver in a young boy with uncomplicated adrenogenital syndrome At operation this proved to be a calcified adrenal cortical adenoma embedded in the right lobe of the liver the major portion of which had to be excised in order to remove the tumor Patient alive and well three years later

upper quadrant incision so modified however as to permit excision of several costal cartilages This exposure permitted excision of the major portion of the right lobe of the liver and the entire tumor (Figure 35) Admittedly this would have been very difficult or impossible through any other type of incision

HORMONAL MANAGEMENT AT OPERATION

We agree wholeheartedly with Kepler and Locke [8] that the management of cases of functioning adrenal tumors is best accomplished by close cooperation between the surgeon and the internist Prior to operation all fore

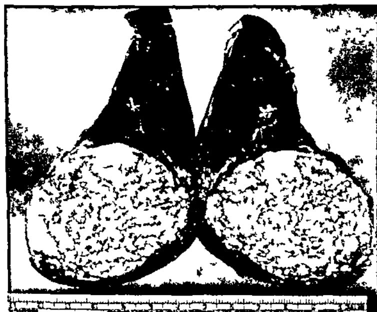


Figure 35 Major portion of right lobe of liver containing an encapsulated calcified adrenal cortical adenoma which was associated with the adrenogenital syndrome in a young boy [147] (Refer to Figure 34)

seeable problems in management are discussed plans agreed upon and preparations made to carry out these plans

Pheochromocytoma

Some difference of opinion exists as to what constitutes optimum hormonal therapy in conjunction with the removal of a pheochromocytoma This revolves around considerations of medullary function few advocating cortical replacement therapy

It has been the experience at The Johns Hopkins Hospital [61] that frequently following removal of a pheochromocytoma the blood pressure falls precipitously and the patient is in a state of shock In recent years this has been successfully combatted in every instance by a continuous intravenous infusion of 5 per cent glucose containing 1 5 mg of epinephrine per 100 cc regulating the rate of flow according to the level of the blood pressure Nothing has been done to counteract the upward swings in pressure incident to manipulation of the tumor prior to removal

Recently Grimson *et al* [48] have reported their experiences in five cases of pheochromocytoma in which an epinephrine competitor regitine® has been injected just before operation and several times prior to actual removal of the tumor in an effort to lower sustained hypertension caused by the tumor or to prevent paroxysms incident to manipulation In the first patient described in an earlier report [43] regitine® effectively prevented paroxysms and postoperative collapse In three of the remaining four although blood pressure was lowered by regitine® prior to removal of the tumor immediately thereafter it was necessary to combat hypotension with pitressin or methedrine®

Howard's [60] philosophy is against the use of competitors during operation He feels that if shock should occur

following removal of the tumor one would be seriously impeded in handling the shock by having the patient full of competitor Furthermore he believes that most competitors so far developed have central nervous system stimulating effects which may confuse the clinical picture

Perhaps the two views can be reconciled and permit one to carry a patient through the entire operation with neither upward nor downward swings in pressure by the use of regitine® prior to removal of the tumor and an infusion of dilute epinephrine immediately thereafter To our knowledge this has not been tried and should first be tried in the animal Certainly long acting competitors such as dibenamine should not be used nor any competitor which cannot be counteracted with epinephrine

Adrenal Cortical Tumors

Short of subtotal or total bilateral adrenalectomy rarely if ever indicated in cases of tumor little in the way of special therapy is needed prior to the day of operation If at exploration it appears probable that in order to effect a cure drastic reduction in the amount of apparently normal adrenal tissue must be accomplished the operation can be terminated and proper premedication instituted several days before the second stage

We have already discussed hormonal therapy in conjunction with the surgical removal of a cortical tumor causing Cushing's syndrome Never having observed atrophy of the contralateral adrenal in cases of adrenogenital syndrome secondary to tumor we have not had to use any cortisone in the postoperative management of these cases Whereas adrenal cortical extract and DCA were used in a few instances we question their value Perhaps with the ready availability of cortisone and because of its low toxicity we should resort to using it routinely in all tumor cases

seeable problems in management are discussed plans agreed upon and preparations made to carry out these plans

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sive survey made in 1950 it was demonstrated conclusively that patients with prostatic cancer who respond favorably to castration and/or estrogen therapy live more comfortably and longer than patients not treated by these methods.[10]

It is equally clear that some patients fail to respond to these forms of treatment and almost all, if not all, eventually relapse. Much work has been done in an effort to learn why. Much of this has implicated the adrenal.

Largely because of the belief that improvement following castration or estrogen administration was attributable to androgen removal or androgen neutralization, it was postulated that in those cases which failed to have a favorable response or in cases that relapsed the adrenals were acting as an extragonadal source of androgen.[69] With this working hypothesis Huggins and Scott[63] in 1945 performed the first total bilateral adrenalectomies in four cases of disseminated prostatic cancer, all previously having relapsed after remissions induced by castration-estrogen therapy. Managed without cortisone, survival times were 1, 3, 11 and 116 days. Obviously no conclusions could be drawn in those surviving only a few days, but in the individual who survived 116 days it appeared as if the prostatic cancer progressed, although apparently at a retarded rate. Following removal of the second adrenal in the individual surviving the longest, urinary 17-ketosteroids fell to very low levels and urinary androgens as measured by the comb growth technic were absent. However, there was a continued excretion of small amounts of estrogen. These hormonal studies coupled with lack of clinical improvement suggested that some prostatic cancers were "androgen independent."

Because of the great difficulty in overcoming adrenal insufficiency with the steroids then available, total bilateral adrenalectomy for widespread prostatic cancer was

VII

BILATERAL ADRENALECTOMY IN THE TREATMENT OF DISSEMINATED CANCER OF THE PROSTATE AND BREAST

INTRODUCTION

IT IS BEYOND the scope of this monograph to review the wealth of evidence which suggests that disseminated cancer of the prostate and breast may be influenced favorably by endocrine measures. Furthermore, at this writing insufficient time has elapsed to permit an accurate evaluation of the measure — *total bilateral adrenalectomy* — which concerns us here. However, because the endocrine approach appears to be the most profitable one at present, a few pages will be devoted to a discussion of this approach to these two cancers.

DISSEMINATED PROSTATIC CANCER

In 1941 Huggins and his associates published three papers under the general heading "Studies on Prostatic Cancer"[0, 68, 0] which dealt primarily with the effects of castration and estrogen administration in metastatic cancer. This work demonstrated that in the majority of instances these endocrine manipulations resulted in subjective and objective improvement. Confirmation by others followed shortly and continues. Thus in an exten

miscellaneous malignant tumors which had metastasized

In the series of seven patients with prostatic cancer studied by Huggins and Bergenstal[5] there was one postoperative death and they judged that three of the remaining six had a clinical remission of the disease of considerable magnitude. One patient died of acute pulmonary edema 49 days after adrenalectomy. The remaining four had been observed for periods of 4½ to nine months at the time of their report. Quoting them again

SUBSTITUTION THERAPY FOR TOTAL ADRENALECTOMY

	0 Minus 1 Day	
Cortisone acetate	50 mg	6 a m 12 noon 6 p m 12 midnight
Desoxycorticosterone acetate	5 mg	6 a m
Sodium chloride	5 gm	6 p m
	0 Day (Day of Operation)	
Cortisone acetate	150 mg	7 a m
Desoxycorticosterone acetate	5 mg	7 a m
Operation †		8 a m
Cortisone acetate	50 mg	Every 4 hr
	0 Plus 1 Day	
Cortisone acetate	50 mg	Every 6 hr
Desoxycorticosterone acetate	5 mg	1 injection
Sodium chloride	3 gm	by mouth
	0 Plus 2 Days	
Cortisone acetate	50 mg	Every 12 hr
Desoxycorticosterone acetate	0 3 mg	As needed
Sodium chloride	3 gm	

Subsequent Days

The dosage of steroids is gradually reduced until the sustaining dose of cortisone acetate (25 to 50 mg daily) is reached about one week after the operation; desoxycorticosterone acetate is not required for maintenance therapy

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Substitution therapy following bilateral adrenalectomy (Courtesy of Dr Charles Huggins and Dr D M Bergenstal)

The cortisone acetate and desoxycorticosterone acetate were administered throughout by intramuscular injection and the sodium chloride by mouth

† Five hundred cubic centimeters of 0 9% sodium chloride and 500 cc of 5% glucose are injected intravenously during operation and 10γ of norepinephrine per cubic centimeter is injected when systolic blood pressure falls below 100 mm

not again performed until early in 1951 [64] In the previous year Harrison Thorn and Criscitiello [3] studying the effect of total bilateral adrenalectomy in malignant hyper tension and chronic nephritis had demonstrated that with judicious use of fluids salt cortisone and desoxycortico sterone acetate it was possible to overcome adrenal in sufficiency and maintain life At the time of their report (May 1951) nine of 15 patients were alive and seven of these were judged improved both subjectively and objec tively They attributed improvement to the elimination of desoxycorticosterone like factors and regulation of its administration thereafter in such a manner as to avoid excessive retention of sodium and water on the one hand and relative hypotension on the other

In June 1951 Huggins and Bergenstal [64] reported on two patients with widespread prostatic cancer who sur vived total adrenalectomy for five and six months and who were in a state of clinical remission at that time The successful substitution therapy which they devised is re produced in Figure 36

Stimulated by this work several different medical groups began studies of the effect of total adrenalectomy not only on prostatic cancer but on other malignant tu mors At the Second National Cancer Conference March 3 4 and 5 of 1952 we learned of many cases some of which have since been reported In February 1952 Hug gins and Bergenstal [6] reported having performed total adrenalectomy in seven men with disseminated pros tatic cancer and in seven women with advanced breast cancer By June 1952 Huggins [63] had done 38 consecu tive total adrenalectomies without an operative fatality Many of these were for metastatic breast cancer in women (*vide infra*) In September 1952 West *et al* [144] published the results of their study of 22 total adrenalectomies 10 in prostatic cancer six in cancer of the breast and six in

chemicals and estrogens considerable work has been done to determine the relation of estrogens to cancer of the breast Space does not permit more than a superficial review of this evidence

In 1916 Lathrop and Loeb[86] demonstrated that the incidence of breast cancer in mice belonging to strains of high incident breast cancer fell to zero in the majority of strains where these mice were oophorectomized at age three to four months Cori showed that this reduction in incidence varied directly with the age of castration — the earlier the castration the lower the incidence If castration was done at the age of eight to 10 months the rate became as high as in the control group However Wooley and co workers[1 3] showed that when female mice of high cancer strains were castrated immediately after birth the incidence of breast tumors was greater than in mice castrated at maturity This phenomenon was thought to be due to the production of estrogen by the adrenal cortex

In 1932 Lacassagne[8] succeeded in producing mammary cancer in males of cancer free strains by the injection of large amounts of estrogenic substances Subsequently he reported induction of mammary cancer in both high and low incident strains but with much greater difficulty in the latter[87] Others have confirmed this work and have extended it to show that the carcinogenic effect of estrogens could be counteracted by androgens Notable among these workers are Raynaud and Lacassagne[11] Murlin and his associates[93] and Nathanson and Adervont[101]

In human breast cancer this principle of utilizing androgens to neutralize the effects of estrogens was voiced simultaneously in 1939 by Loeser[5] and by Ulrich[133] These authors described favorable changes in patients with advanced breast cancer following the administration

Perhaps the most striking observation has been the immediate and persistent relief of crippling pain in the bones

The most recent results in the series of 10 patients adrenalectomized for prostatic cancer and reported by West and his associates[144] are in an addendum to their paper Three died in the immediate postoperative period one from cerebral hemorrhage (two days) one from carcinomatosis (11 days) and one from myocardial infarction (21 days) Six of the remaining seven died within 33 to 294 days after adrenalectomy two from adrenal insufficiency and four from cancer The remaining patient was living at the writing of the addendum his 159th postoperative day According to the authors All seven patients had temporary subjective improvement varying from 14 to 210 days averaging 82 days Only two out of the seven had objective improvement lasting 90 to 133 days Quoting further The most striking beneficial response to adrenalectomy was relief of pain

Our own experience is similar (unpublished)

Needless to say the merits of endocrine management will be decided not on any theoretical basis but on its practical value The belief that these procedures are effective though not curative drives us to study the possible mechanisms involved in the hope that further advances can be made Those interested in a discussion of possible mechanisms are referred to a rather lengthy account by one of us[1,1]

DISSEMINATED BREAST CANCER

Largely as the result of the association of breast growth and development with ovarian activity and the demonstration of a relationship between certain carcinogenic

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DISSEMINATED BREAST CANCER

Largely as the result of the association of breast growth and development with ovarian activity and the demonstration of a relationship between certain carcinogenic

presented elsewhere and will not be considered here Huggins later report with Dao [66] follows the seven patients originally reported for a longer time and hence is more informative One more case is added Of the eight one died 48 hours after operation Of the remaining seven two had no response to therapy and died at 34 days and six months respectively Five were living for periods of seven to 11 months and four of these were judged to have had a satisfactory response

The results of West *et al* [144] are similar Of the five cases with breast cancer three are now dead All three died from their neoplastic disease The post operative survival in these cases varied from 119 to 170 days averaging 137 days Two cases are still alive 169 and 175 days postoperatively Both of these cases had subjective and objective improvement for approximately 120 days Both patients showed objective improvement All five patients showed subjective improvement lasting from 14 to 120 days averaging 67 days

The search goes on

of testosterone propionate This therapeutic method was applied extensively after the publication of Adair and Herrmann

In 1944 Binnie[1] in an effort to make advanced breast cancer in the female more radiosensitive noted regression of the tumor in a patient by the use of estrogen alone (diethylstilbestrol) Haddow *et al*[1] subsequently noted favorable changes in 16 of 40 patients treated with estrogen alone Two years later Nathanson[100] reported definitely favorable to excellent results in 28 of 54 women with advanced cancer of the breast treated with relatively large doses of estrogen

Since the publications of Adair and Herrmann and Nathanson[100] literally thousands of women with inoperable breast cancers have been treated with either androgens or estrogens Generally speaking androgens have been more effective in the premenopausal woman and have had a greater effect on skeletal lesions Improvement following estrogen usually given after the menopause has consisted primarily of changes in the local *lesion and in lymph node and pulmonary metastases*

On the basis of experimental data in animals it is difficult to reconcile the apparently paradoxical effects of estrogen in human breast cancer Theoretically androgen should work better than estrogen Differences in response may be related to many factors which include the age of the patient the size of the dose of hormone given the state of other endocrine glands and the phase of the cancer Huggins[61] states Both methods of treatment are empirical

Recognizing that other factors may be involved as stated above Huggins and Bergenstal[6] carried out bilateral adrenalectomy in seven women with advanced breast cancer The theoretical considerations forming the basis for this type of therapy as developed by them are

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SUBJECT INDEX

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By William Wallace Scott, M.D., Ph.D. *and* Perry B. Hudson, M.D.

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